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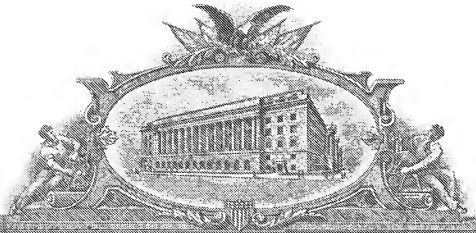

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APPLICATION NUMBER: ***60/544,376***
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PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c)

Express Mail Label No. **EL 996371331 US**

INVENTOR(S)		
Given Name (first and middle [if any])	Family Name or Surname	Residence (City and either State or Foreign Country)
David S.	**Lawrence**	**Hartsdale, New York**

Additional inventors are being named on the _____ *separately numbered sheets attached hereto*

TITLE OF THE INVENTION (500 characters max)

PROTEIN KINASE INHIBITORS AND METHODS FOR IDENTIFYING SAME

Direct all correspondence to: **CORRESPONDENCE ADDRESS**

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OR

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ENCLOSED APPLICATION PARTS *(check all that apply)*

☑ Specification *Number of Pages* **51**
☑ Drawing(s) *Number of Sheets* **205**
☐ Application Date Sheet. See 37 CFR 1.76
☐ CD(s), Number _____
☑ Other (specify) specification cover page; cover letter; return receipt postcard

METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT

☑ Applicant claims small entity status. See 37 CFR 1.27.
☑ A check or money order is enclosed to cover the filing fees.
☑ The Director is hereby authorized to charge **additional** fees or credit any overpayment to Deposit Account Number: **01-1785**
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The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

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Respectfully submitted,

SIGNATURE _____

TYPED or PRINTED NAME **Elie H. Gendloff**

TELEPHONE **212-336-8000**

Date **February 13, 2004**

REGISTRATION NO. **44,704** *(if appropriate)*

Docket Number: **96700/842**

USE ONLY FOR FILING A PROVISIONAL APPLICATION FOR PATENT

This collection of information is required by 37 CFR 1.51. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 8 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: **Mail Stop Provisional Application, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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February 13, 2004

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"Express Mail" mailing label No. EL 996371331 US
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I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to the Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.
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Mail Stop Provisional Patent Application
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Re: Rule 1.53(c) Provisional Patent Application Claiming Small Entity Status
Title: PROTEIN KINASE INHIBITORS AND METHODS FOR IDENTIFYING SAME
Inventor: David S. Lawrence
Our File: 96700/842

Dear Sir:

Pursuant to 37 C.F.R. §1.53(c), enclosed please find the following documents for filing with the above-identified provisional patent application claiming small entity status in the name of David S. Lawrence, entitled PROTEIN KINASE INHIBITORS AND METHODS FOR IDENTIFYING SAME, comprising the following:

1. Provisional Application For Patent Cover Sheet (Form PTO/SB/16) (1 page);

2. Provisional patent application, including: application cover page (1 page), specification (33 pages), claims (17 pages), abstract (1 page), and drawings (205 sheets);

3. Amster, Rothstein & Ebenstein LLP check in the amount of $80.00 to cover the provisional application filing fee for small entity status; and

4. Return receipt postcard.

Please acknowledge receipt of the enclosed papers by stamping the enclosed postcard and returning the same to us.

Respectfully submitted,

AMSTER, ROTHSTEIN & EBENSTEIN LLP
Attorneys for Applicant
90 Park Avenue
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212 336 8000

Dated: February 13, 2004
New York, New York

By: _____
Elie H. Gendloff
Registration No. 44,704

AR&E Docket No. 96700/842

New U.S. Provisional Patent Application (Small Entity Status)

Title: PROTEIN KINASE INHIBITORS AND METHODS FOR IDENTIFYING SAME

Inventor: David S. Lawrence

Express Mail EL 996371331 US

AR&E Docket No. 96700/842

PROTEIN KINASE INHIBITORS AND METHODS FOR IDENTIFYING SAME

Background

(1) Field of the Invention

The present invention generally relates to enzyme inhibitors and methods of discovering them. More particularly, the invention is directed to protein kinase inhibitors and methods using combinatorial libraries for identifying protein kinase inhibitors.

(2) Description of the Related Art

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U.S. Patent No. 6,214,852.

U.S. Patent No. 6,248,559.

U.S. Patent No. 6,376,747.

U.S. Patent No. 6,660,731.

Signal transduction is the biochemical mechanism by which information is transmitted between distinct cellular sites. Signaling pathways differ from their classical biochemical counterparts in a number of ways. For example, the enzymes of glycolysis and the TCA cycle catalyze the conversion of small molecules into products, which are then passed onto the next enzymatic member of the pathway. By contrast, the protein participants of signaling pathways primarily associate with and act upon one another.

An important group of eukaryotic and viral enzymes involved in these signaling pathways are protein kinases. Protein kinases are enzymes that transfer a phosphate group from a donor molecule, usually ATP, to an amino acid residue of a protein. In signal transduction, this protein phosphorylation can activate or inhibit the activity of the protein. Types of protein kinases include serine/threonine-specific protein kinases such as phosphorylase kinase, protein kinase A, protein kinase C, Ca^{2+}/calmodulin -dependent protein kinase, MAP kinase, and Mos/Raf kinase; tyrosine-specific protein kinases such as receptor tyrosine kinase; histidine-specific protein kinases; and aspartic acid/glutamic acid-specific protein kinases.

Several deleterious conditions (including diseases) are associated with expression of protein kinases. These deleterious conditions include various cancers, various cardiovascular diseases, type 2 diabetes, agammaglobulinaemia, reperfusion injury, Alzheimer's disease, various neurological and neurodegenerative diseases, chemotherapy-induced alopecia, arthritis, various autoimmune diseases, various inflammatory diseases, allergies, asthma and viral virulence (Inagaki et al., 2003; Wang et al., 2003; Lahn et al., 2003, 2004; Neid et al. 2003; Vetrie et al., 1993; Stenberg et al., 2000; Munger and Roizman, 2001; U.S. Patent Nos. 6,248,559; 6,214,852; 6,660,731).

Protein kinase C (PKC) is a family of protein kinases that generally require Ca^{2+}, diacylglycerol (DAG) and a phospholipids such as phosphatidylcholine for activation. There are at least 11 isoforms (=isozymes) of mammalian PKC - α, βI, βII, γ, δ, ε, ζ, η, 0, τ/λ, and μ which vary by tissue distribution, activators and substrates.

PKCs are further classified as classical or conventional PKC (α, βI, βII and γ), which require phospholipid, DAG or phorbol ester, and Ca^{2+} for activation; novel PKC (δ, ε, η and θ), requiring phospholipid, DAG or phorbol ester, but not Ca^{2+}, and atypical PKC (ζ, and τ/λ), requiring phospholipid, but not DAG, phorbol ester, or Ca^{2+}. Structural differences also distinguish these three groups of PKC from each other.

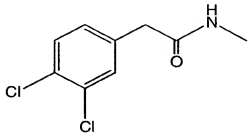
PKCs are known to be involved in many cellular functions, including cell proliferation, tumor promotion, differentiation, and apoptotic cell death. For a review of PKC structure and function, see Musashi et al., 2000.

The amino acid sequences ("consensus recognition sequences") that drive critical protein-protein kinase interactions are readily identified using combinatorial peptide-based libraries (Lam et al., 2003; Cortese et al., 1995; Dostmann et al., 2002; Chan et al., 1998). Consensus sequence information has proven helpful in piecing together signaling pathways. In addition, peptides containing these sequences are potentially useful inhibitory reagents that could furnish information about the biological role of signaling proteins. Unfortunately, consensus sequence peptides tend to display modest affinities (K_D or K_i > low μM) for their protein targets. We (Yeh et al., 2002; Yeh et al., 2001; Shen et al., 2001; Lee et al., 1999), as well as others (See, e.g., Nguyen et al., 2000; Feng et al., 1996), have shown that consensus sequences for signaling proteins can be converted into higher affinity ligands using the 3-dimensional structure of the protein target as a guide. Nevertheless, the tertiary structure for only a small minority of all signaling proteins has been assigned, thereby limiting the generality of this approach. There is thus a need for procedures for identification of inhibitors of protein kinases. The present invention addresses that need.

Summary of the Invention

Accordingly, the inventors have discovered methods for identifying protein kinase inhibitors using combinatorial libraries utilizing a consensus sequence of the protein kinase. The inventors used these methods to identify potent and selective inhibitors of protein kinase C (PKC) α, PKCδ, and PKCζ.

Thus, in some embodiments, the invention is directed to inhibitors of protein kinase Cα (PKCα). The inhibitors comprise A-Ala-Arg-Arg-X-B-Hyd-C-D-, where A =AcHN-,



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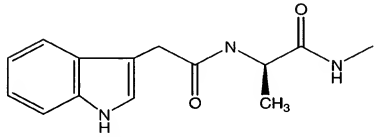

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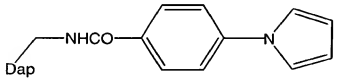
X=any amino acid or amino acid mimetic; B=Ala or a diaminopropionic acid (Dap) derivative having the formula



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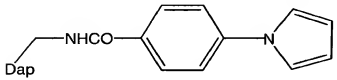
Hyd=Phe, Leu or Ile; C=Arg or Lys; and D=Ala or a Dap derivative having the formula



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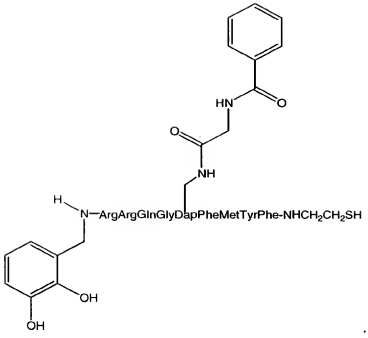
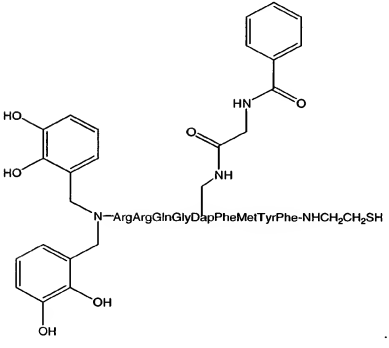
wherein any of the amino acids can alternatively be an analogous amino acid mimetic.

The invention is also directed to inhibitors of protein kinase Cδ (PKCδ). These inhibitors comprise



The present invention is additionally directed to inhibitors of protein kinase Cζ (PKCζ). These inhibitors comprise



In additional embodiments, the invention is directed to compositions comprising any of the above inhibitors, in a pharmaceutically acceptable excipient.

The present invention is also directed to combinatorial libraries useful for identifying an inhibitor of a protein kinase. The combinatorial libraries comprise a plurality of

compounds, each compound comprising a consensus sequence for a substrate of the protein kinase, the consensus sequence comprising at least five amino acids or mimetics, wherein at least one amino acid or mimetic is not essential to substrate binding, and wherein an amino acid or mimetic not subject to phosphorylation substitutes a canonical Ser or Thr target residue in the consensus sequence; and a chemical moiety covalently bound to the compound at the at least one non-essential amino acid or mimetic in the consensus sequence and/or the amino acid or mimetic not subject to phosphorylation substituting the canonical Ser or Thr target residue. In these combinatorial libraries, each compound comprises a different chemical moiety.

In further embodiments, the present invention is directed to methods of identifying an inhibitor of a protein kinase. The methods comprise creating a combinatorial library as described above for the protein kinase, screening the compounds in the combinatorial library for inhibitory activity of the protein kinase, and identifying any compounds in the combinatorial library that are inhibitors of the protein kinase.

The invention is additionally directed to methods of treating a deleterious condition in a mammal that is dependent on a protein kinase for induction or severity. The methods comprise contacting the mammal with an inhibitor of the protein kinase found by any of the above-described methods of identifying an inhibitor of a protein kinase.

The invention is further directed to methods of inhibiting a protein kinase. The methods comprise contacting the protein kinase with an inhibitor of the protein kinase identified by any of the above-described methods of identifying an inhibitor of a protein kinase.

In other embodiments, the invention is directed to the use of an inhibitor of a protein kinase in the manufacture of a medicament for the treatment of a deleterious condition in a mammal that is dependent on a protein kinase for induction or severity. The treatment comprises contacting the mammal with an inhibitor of the protein kinase found any of the above-described methods of identifying an inhibitor of a protein kinase.

Brief Description of the Drawings

FIG. 1 shows libraries **I – IV** used to identify inhibitors of protein kinase Cα (PKCα).

FIG. 2 shows various compounds used in PKCα inhibitor studies.

FIG. 3 is a graph of the inhibition pattern of compound 3 versus variable [ATP].

FIG. 4 shows 720 carboxylic acid moieties used in exemplified invention combinatorial libraries.

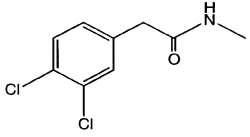
FIG. 5 shows 54 aldehyde moieties used in exemplified invention combinatorial libraries.

Detailed Description of the Invention

The present invention is based on the discovery of methods for identifying protein kinase inhibitors using combinatorial libraries utilizing a consensus sequence of the protein kinase. As described in Examples 1 and 2, the inventors proved the utility of these methods by using them to identify potent and selective inhibitors of protein kinase C (PKC) α, PKCδ, and PKCζ.

Thus, in some embodiments, the invention is directed to inhibitors of protein kinase Cα (PKCα). The inhibitors comprise

A-Ala-Arg-Arg-X-B-Hyd-C-D-, where A =AcHN-,



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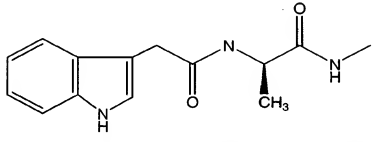

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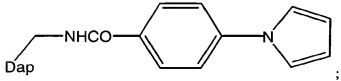
X=any amino acid or amino acid mimetic; B=Ala or a diaminopropionic acid (Dap) derivative having the formula



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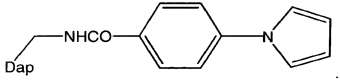
Hyd=Phe, Leu or Ile; C=Arg or Lys; and D=Ala or a Dap derivative having the formula



In the above formula, and throughout this application, three letter amino acid abbreviations take on their usual meaning as L-amino acids, as well as analogous amino acid mimetics, unless otherwise specified.

As used herein, an amino acid mimetic is an amino acid analog that can mimic the biological action of the amino acid. Preferred examples include D-amino acids (including natural and artificial [e.g., Dap] amino acids) and other mimetics with non-hydrolyzable peptide bonds. As used herein, non-hydrolyzable means that the bonds linking the amino acids of the peptide are less readily hydrolyzed, e.g., by proteases, than peptide bonds formed between L-amino acids. Susceptibility to proteolytic cleavage can be determined without undue experimentation, for example by labeling peptides and incubating the labeled peptides with cell extracts or purified proteases, then isolate the treated peptides to determine which peptide bonds are susceptible to proteolysis, e.g., by sequencing peptides and proteolytic fragments. Alternatively, potentially susceptible peptide bonds can be identified by comparing the amino acid sequence of an isolated peptide with the known cleavage site specificity of a panel of proteases. Based on the results of such assays, individual peptide bonds which are susceptible to proteolysis can be replaced with non-hydrolyzable peptide bonds by in vitro synthesis of the peptide.

Many non-hydrolyzable peptide bonds are known in the art, along with procedures for synthesis of peptides containing such bonds. Non-hydrolyzable bonds include -CH_2NH- (reduced amide peptide bonds), -OCH_2- (ketomethylene peptide bonds), -CH(CN)NH- ((cyanomethylene)amino peptide bonds), -$CH_2CH(OH)$- (hydroxyethylene peptide bonds), -CH_2O-, and -CH_2S- (thiomethylene peptide bonds).

In the inhibitors of the present invention, any one or more than one of the amino acid moieties can be a mimetic. Preferably, the mimetic moieties permit the peptide to retain its natural conformation, or stabilize a bioactive conformation. One example of methods for preparation of nonpeptide mimetic analogs from peptides is described in Nachman et al., 1995.

Because the non-amino acid constituents of these inhibitors have a large and critical influence on their inhibitory activity (Example 1), it is believed that mimetic substitutions for the amino acid moieties would have little effect on the inhibitory activity of the inhibitors.

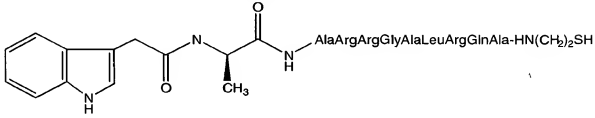
These inhibitors may further comprise constituents conjugated to any of the amino acid or mimetic moieties, as may be useful for detection, isolation, or quantitation of the inhibitor or its binding partners, such as PKCδ. Examples of such constituents include a His-6 moiety, a fluorescent moiety or a radioactive moiety.

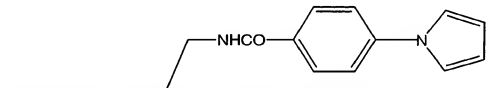
The inhibitor of these embodiments preferably have a PKCα IC_{50}<50 μM. The IC_{50} for any of the invention inhibitors can be determined without undue experimentation, for example by the methods described in Example 1. In more preferred embodiments, the inhibitor has a PKCα IC_{50}<10 μM; in even more preferred embodiments, the inhibitor has a PKCα IC_{50}<1 μM; in the most preferred embodiments, the inhibitor has a PKCα IC_{50}<0.1 μM.

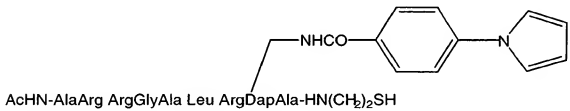
It is also preferred that the inhibitor is specific for a PKCα. As used herein, an inhibitor is specific for a PKCα if the inhibitor has an IC_{50} for a PKCα<0.5 that of any other PKC isoform. Preferably, the inhibitor has an IC_{50} for a PKCα<0.1 that of any other PKC isoform. More preferably, the inhibitor has an IC_{50} for a PKCα<0.01 that of any other PKC isoform.

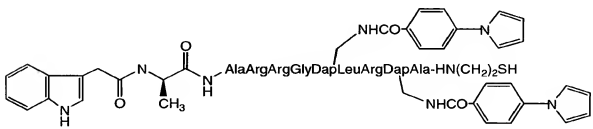
The inhibitors of these embodiments would be expected to have similar inhibitory activity for any mammalian PKCα, including a human, a rodent, or a chimeric or otherwise novel PKCα.

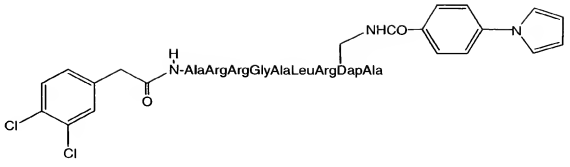
In preferred embodiments, the inhibitors comprise, or consist of,











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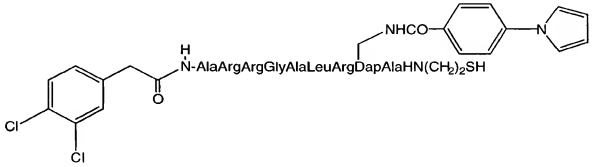
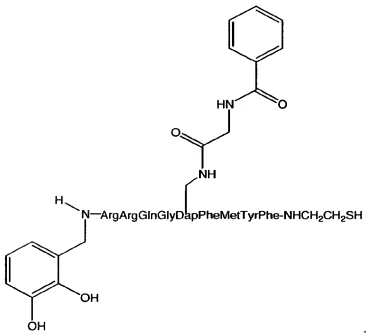


(See Example 1).

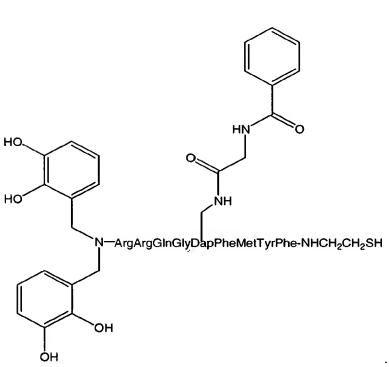
The invention is also directed to inhibitors of protein kinase Cδ (PKCδ), the inhibitors comprise, or consist of,



As shown in Example 2, these inhibitors are highly specific and have strong inhibitory activity for PKCδ (IC_{50}=18 nM). As with the previous inhibitors, the amino acid constituents

of these inhibitors can also be mimetics. Also, these inhibitors may further comprise constituents conjugated to any of the amino acid or mimetic moieties, as may be useful for detection, isolation, or quantitation of the inhibitor or its binding partners, e.g., PKCδ.

In further embodiments, the invention is directed to inhibitors of protein kinase Cζ (PKCζ). The inhibitors comprise, or consist of,



As shown in Example 2, these inhibitors are highly specific and have strong inhibitory activity for PKCζ (IC_{50}=7.5 nM). As with the previous inhibitors, the amino acid constituents of these inhibitors can also be mimetics. Also, these inhibitors may further comprise constituents conjugated to any of the amino acid or mimetic moieties, as may be useful for detection, isolation, or quantitation of the inhibitor or its binding partners, e.g., PKCζ.

Any of the above-described inhibitors can be formulated without undue experimentation for administration to a mammal, including humans, as appropriate for the particular application. Additionally, proper dosages of the inhibitor compositions can be determined without undue experimentation using standard dose-response protocols.

Accordingly, the inhibitor compositions designed for oral, lingual, sublingual, buccal and intrabuccal administration can be made without undue experimentation by means well known in the art, for example with an inert diluent or with an edible carrier. The inhibitor compositions may be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the inhibitor compositions of the present invention may be

incorporated with excipients and used in the form of tablets, troches, capsules, elixirs, suspensions, syrups, wafers, chewing gums and the like.

Tablets, pills, capsules, troches and the like may also contain binders, recipients, disintegrating agent, lubricants, sweetening agents, and flavoring agents. Some examples of binders include microcrystalline cellulose, gum tragacanth or gelatin. Examples of excipients include starch or lactose. Some examples of disintegrating agents include alginic acid, corn starch and the like. Examples of lubricants include magnesium stearate or potassium stearate. An example of a glidant is colloidal silicon dioxide. Some examples of sweetening agents include sucrose, saccharin and the like. Examples of flavoring agents include peppermint, methyl salicylate, orange flavoring and the like. Materials used in preparing these various compositions should be pharmaceutically pure and nontoxic in the amounts used.

The inhibitor compositions of the present invention can easily be administered parenterally such as for example, by intravenous, intramuscular, intrathecal or subcutaneous injection. Parenteral administration can be accomplished by incorporating the inhibitor compositions into a solution or suspension. Such solutions or suspensions may also include sterile diluents such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents. Parenteral formulations may also include antibacterial agents such as for example, benzyl alcohol or methyl parabens, antioxidants such as for example, ascorbic acid or sodium bisulfite and chelating agents such as EDTA. Buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose may also be added. The parenteral preparation can be enclosed in ampules, disposable syringes or multiple dose vials made of glass or plastic.

Rectal administration includes administering the pharmaceutical inhibitor compositions into the rectum or large intestine. This can be accomplished using suppositories or enemas. Suppository formulations can easily be made by methods known in the art. For example, suppository formulations can be prepared by heating glycerin to about 120° C., dissolving the inhibitor composition in the glycerin, mixing the heated glycerin after which purified water may be added, and pouring the hot mixture into a suppository mold.

Transdermal administration includes percutaneous absorption of the inhibitor composition through the skin. Transdermal formulations include patches (such as the well-known nicotine patch), ointments, creams, gels, salves and the like.

The present invention includes nasally administering to the mammal a therapeutically effective amount of the composition. As used herein, nasally administering or nasal administration includes administering the inhibitor composition to the mucous membranes of the nasal passage or nasal cavity of the patient. As used herein, pharmaceutical compositions for nasal administration of an inhibitor composition include therapeutically effective amounts

of the composition prepared by well-known methods to be administered, for example, as a nasal spray, nasal drop, suspension, gel, ointment, cream or powder. Administration of the inhibitor composition may also take place using a nasal tampon or nasal sponge.

The above-identified protein kinase inhibitors were discovered using novel combinatorial libraries. These combinatorial libraries have the advantage of not requiring information about the structure of the active site of the enzyme.

Thus, the invention is also directed to combinatorial libraries useful for identifying an inhibitor of a protein kinase. The combinatorial libraries comprise a plurality of compounds, each compound comprising the following elements:

- a consensus sequence for a substrate of the protein kinase, the consensus sequence comprising at least five amino acids or mimetics, wherein at least one amino acid or mimetic is not essential to substrate binding, and wherein an amino acid or mimetic not subject to phosphorylation substitutes a canonical Ser or Thr target residue in the consensus sequence; and

- a chemical moiety covalently bound to the compound at the at least one non-essential amino acid or mimetic in the consensus sequence and/or the amino acid or mimetic not subject to phosphorylation substituting the canonical Ser or Thr target residue. Each of the compounds in the combinatorial library comprises a different chemical moiety.

In preferred embodiments, the non-essential amino acid or mimetic and/or the amino acid or mimetic substituting a canonical Ser or Thr target residue is a diaminopropionic acid (Dap), because the various chemical moieties conjugated to the compound can be easily conjugated thereto, for example using a carboxyl or aldehyde derivative of the chemical moiety, which can be conjugated to the free amino group of the Dap by known methods. However, other compounds can substitute for the non-essential amino acid and/or the amino acid or mimetic substituting a canonical Ser or Thr target residue, preferably compounds that allow convenient conjugation of the chemical moieties thereto.

In some embodiments, the chemical moiety conjugated to each compound is a carboxylic acid. See Example 1. Such carboxylic acids can, for example, be selected from any one of the carboxylic acids provided in FIG. 4.

In other embodiments, the chemical moiety conjugated to each compound is an aldehyde. See Example 2. Such aldehydes can, for example be selected from any of the aldehydes provided in FIG. 5.

Two or more chemical moieties can be conjugated to the consensus sequence portion of the compound. See, e.g., the above-described inhibitors for PKCδ and PKCζ, which contain one chemical moiety from a carboxylic acid and one from an aldehyde.

The chemical moieties are selected to add a diverse range of shapes and charges to the consensus sequence. For example, conjugating the carboxylic acid moiety to the consensus sequence to a Dap results in an amide bond, which is neutral under physiological conditions. By contrast, with aldehydes one obtains an alkylated amine, which is positively charged under physiological conditions.

The amino acid or mimetic not subject to phosphorylation that substitutes a canonical Ser or Thr target residue in the consensus sequence can comprise any amino acid or mimetic, whether natural or artificial. In preferred embodiments, this amino acid or mimetic is a Dap or an Ala.

These combinatorial libraries can be used to identify an inhibitor of any protein kinase from any species, including any eukaryote or virus. Preferably, the protein kinase is a mammalian protein kinase, such as a human protein kinase. Included are any types of protein kinases, such as serine/threonine-specific protein kinases (phosphorylase kinase, protein kinase A, protein kinase C, Ca^{24}/calmodulin -dependent protein kinase, MAP kinase, and Mos/Raf kinase), tyrosine-specific protein kinases such as receptor tyrosine kinase, histidine-specific protein kinases, and aspartic acid/glutamic acid-specific protein kinases. In preferred embodiments, the protein kinase is a protein kinase C (PKC).

In some of these embodiments, the PKC is PKCα. Where the PKC is PKCα, a preferred consensus sequence comprises LysGlySerHyd(Arg/Lys), where Hyd is Phe, Leu or Ile. In those embodiments, a preferred consensus sequence having an Ala substituting for the canonical Ser or Thr target residue is AlaArgArgGlyAlaLeuArgGlnAla.

In other embodiments, the protein kinase is PKCβI and the consensus sequence comprises ArgLysGlySerPheLys; the protein kinase is PKCβII and the consensus sequence comprises ArgLysGlySerPheLys; the protein kinase is PKCγ and the consensus sequence comprises ArgLysGlySerPheLys; the protein kinase is PKCδ and the consensus sequence comprises (Lys/Gln)GlySerPhe(Phe/Met); the protein kinase is PKCε and the consensus sequence is Lys(Met/Lys)Ser(Phe/Ala)(Glu/Tyr/Asp/Phe); the protein kinase is PKCη and the consensus sequence is ArgArgSerPheArgArg; the protein kinase is PKCζ and the consensus sequence is (Arg/Gln/Lys/Glu)(Met/Gly)Ser(Phe/Met)(Phe/Met); or the protein kinase is PKCμ and the consensus sequence is (Gln/Lys/Glu/Met)MetSer(Val/Met/Leu)(Ala/Met/Val).

In preferred embodiments, the combinatorial library comprises at least 10 compounds. More preferably, the combinatorial library comprises at least 50, or 100, or 200, or 300, or 400, or 500 compounds.

The invention is also directed to methods of identifying an inhibitor of a protein kinase. The methods comprise creating a combinatorial library as described above for the

protein kinase, screening the compounds in the combinatorial library for inhibitory activity of the protein kinase, and identifying any compounds in the combinatorial library that are inhibitors of the protein kinase.

These methods can be used to identify an inhibitor of any eukaryotic or viral protein kinase now known or later discovered, including any mammalian, plant, insect, or protist protein kinase.

In preferred embodiments of these methods, two combinatorial libraries are created and screened for inhibitory activity. The first combinatorial library is created and used to identify a lead compound with some inhibitory activity. The second library is then created where all members have the chemical moiety of the lead compound and additional chemical moieties. As shown in Examples 1 and 2, this strategy can be successful in identifying potent inhibitors with high specificity.

The screening method can utilize any procedure known in the art for measuring inhibitory activity for the particular protein kinase. See, e.g., Example 1. The screening methods can also include a determination of the specificity of the inhibitory activity for any isoform of the protein kinase target, or for any other enzyme or bioactive compound. In preferred embodiments, specificity determinations are performed only on compounds that show sufficient inhibitory activity for the target protein kinase.

With these methods, the compounds can be screened separately. Alternatively, more than one inhibitor can be initially screened together, e.g., in batches, then the individual compounds from any batch that shows inhibitory activity are further tested.

Any of these methods can be adapted to automated or robotic procedures.

In preferred embodiments of these methods, the protein kinase is a protein kinase C (PKC), for example PKCα, a PKCδ, or a PKCζ.

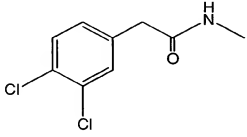
Protein kinases are known to be involved in various deleterious conditions, for example, various cancers, various cardiovascular diseases, type 2 diabetes, agammaglobulinaemia, reperfusion injury, Alzheimer's disease, various neurological and neurodegenerative diseases, chemotherapy-induced alopecia, arthritis, various autoimmune diseases, various inflammatory diseases, allergies, asthma and viral virulence (Inagaki et al., 2003; Wang et al., 2003; Lahn et al., 2003, 2004; Neid et al. 2003; Vetrie et al., 1993; Stenberg et al., 2000; Munger and Roizman, 2001; U.S. Patent Nos. 6,248,559; 6,214,852; 6,660,731). Therefore, the administration of inhibitors described herein to mammals having or at risk for such deleterious conditions would be expected to be useful treatments for those conditions.

Thus, the present invention is additionally directed to methods of treating a deleterious condition in a mammal, where the condition is dependent on a protein kinase for induction or

severity. The methods comprise contacting the mammal with an inhibitor of the protein kinase found by the above-described methods of identifying an inhibitor of the protein kinase.

In preferred embodiments of these methods, the protein kinase is a protein kinase C (PKC). Where the protein kinase is PKCα, the preferred inhibitor comprises

A-Ala-Arg-Arg-X-B-Hyd-C-D-, where A- =AcHN-,



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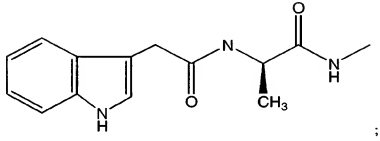

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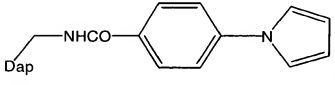
X=any amino acid or amino acid mimetic; B=Ala or a diaminopropionic acid (Dap) derivative having the formula



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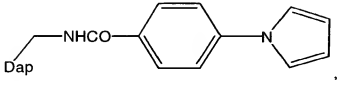
Hyd=Phe, Leu or Ile; C=Arg or Lys; and D=Ala or a Dap derivative having the formula



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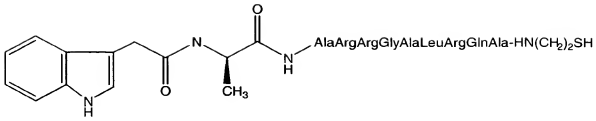
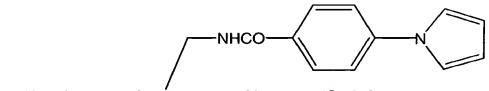
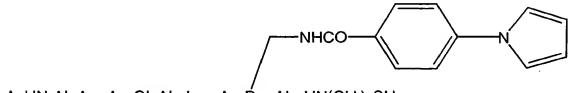
wherein any of the amino acids can alternatively be an analogous amino acid mimetic.

Preferred examples of such inhibitors are


AlaArgArgGlyAlaLeuArgGlnAla-HN(CH2)2SH


NHCO
AcHN-AlaArg ArgGlyDapLeuArgGlnAla-HN(CH2)2SH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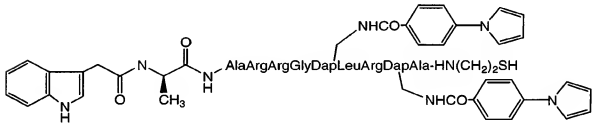
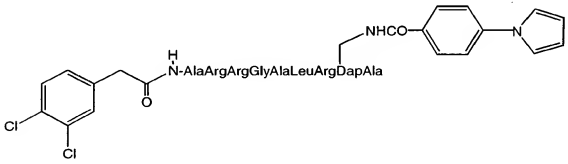
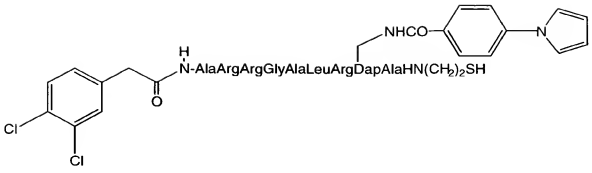
AcHN-AlaArg ArgGlyAla Leu ArgDapAla-HN(CH2)2SH

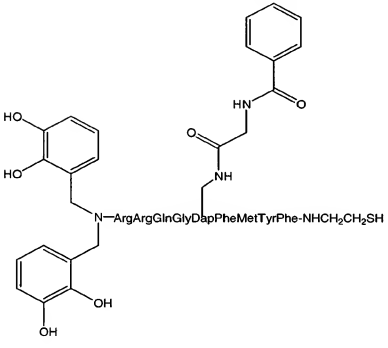

NHCO
AlaArgArgGlyDapLeuArgDapAla-HN(CH2)2SH
NHCO


NHCO
N-AlaArgArgGlyAlaLeuArgDapAla

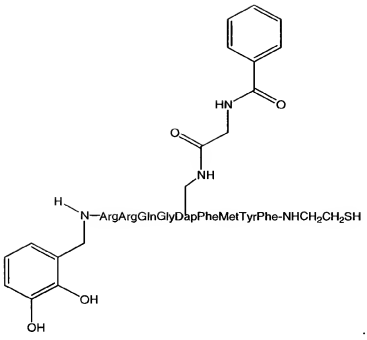
and



Where the protein kinase is PKCδ, a preferred inhibitor is



Additionally, where the protein kinase is PKCζ, a preferred inhibitor is



In any of these embodiments, the inhibitor is preferably in a pharmaceutically acceptable excipient, as previously described.

The deleterious condition can be any condition that is dependent on a protein kinase for induction or severity. Preferred examples include cancer, cardiovascular disease, type 2 diabetes, agammaglobulinaemia, reperfusion injury, Alzheimer's disease, neurological or neurodegenerative disease, chemotherapy-induced alopecia, arthritis, autoimmune disease, inflammatory disease, allergies, asthma and viral virulence. In more preferred embodiments, the deleterious condition is a cancer, a cardiovascular disease, or type 2 diabetes.

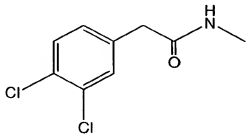
These methods are useful for treatment of any mammal, for example a rodent or a human.

The present invention is also directed to methods of inhibiting a protein kinase. The methods comprise contacting the protein kinase with an inhibitor of the protein kinase identified by the methods of identifying an inhibitor of a protein kinase described above. These methods could be used to inhibit a protein kinase that is isolated, or, preferably, in a living mammalian cell. Where the protein kinase is in a living cell, the cell can be in culture or in a living mammal, such as a rodent or a human. Such a mammal can additionally have a deleterious condition that is dependent on the protein kinase for induction or severity. As discussed above, such deleterious conditions include various cancers, various cardiovascular diseases, type 2 diabetes, agammaglobulinaemia, reperfusion injury, Alzheimer's disease, various neurological and neurodegenerative diseases, chemotherapy-induced alopecia, arthritis, various autoimmune diseases, various inflammatory diseases, allergies, asthma and viral

virulence. include cancer, heart disease or type 2 diabetes. In more preferred embodiments, the deleterious condition is a cancer, a cardiovascular disease, or type 2 diabetes.

In preferred embodiments, the protein kinase is a protein kinase C (PKC). Where the protein kinase is PKCα, the inhibitor preferably comprises

A-Ala-Arg-Arg-X-B-Hyd-C-D-, where A- =AcHN-,



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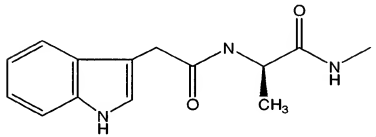

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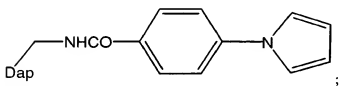
X=any amino acid or amino acid mimetic; B=Ala or a diaminopropionic acid (Dap) derivative having the formula



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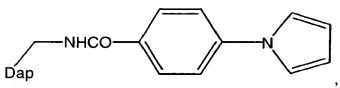
Hyd=Phe, Leu or Ile; C=Arg or Lys; and D=Ala or a Dap derivative having the formula



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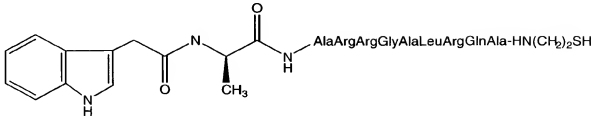
wherein any of the amino acids can alternatively be an analogous amino acid mimetic.

Preferred examples of such inhibitors include



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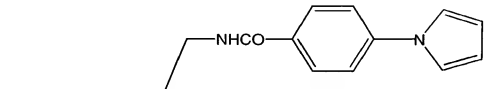

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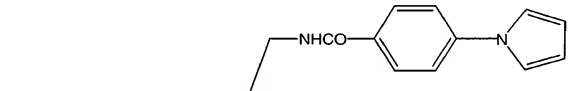

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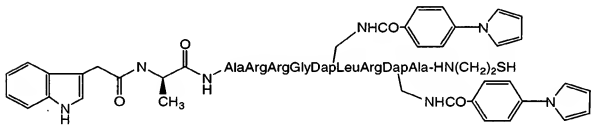

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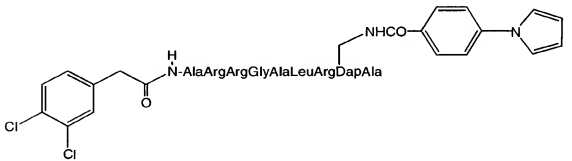

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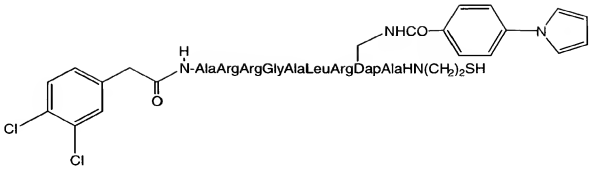
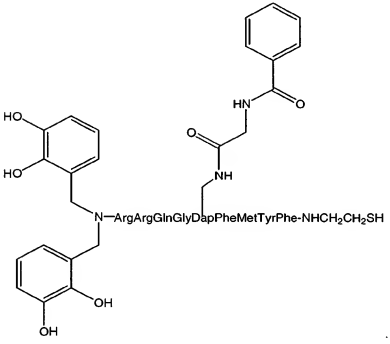
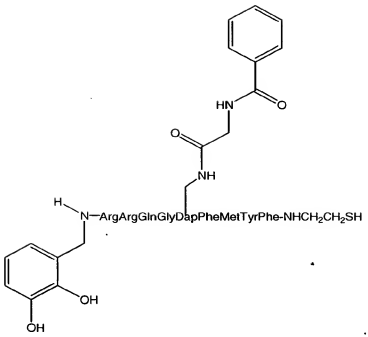


Where the protein kinase is a PKCδ, the inhibitor is preferably



Where the protein kinase is PKCζ, the inhibitor is preferably



In additional embodiments, the invention is directed to the use of an inhibitor of a protein kinase in the manufacture of a medicament for the treatment of a deleterious condition in a mammal that is dependent on a protein kinase for induction or severity. The treatment comprises contacting the mammal with an inhibitor of the protein kinase identified by the methods of identifying an inhibitor of a protein kinase described above.

Preferred embodiments of the invention are described in the following examples. Other embodiments within the scope of the claims herein will be apparent to one skilled in the art from consideration of the specification or practice of the invention as disclosed herein. It is intended that the specification, together with the examples, be considered exemplary only, with the scope and spirit of the invention being indicated by the claims which follow the examples.

Example 1. Inhibitors of Protein Kinase Cα and Methods of Identifying Those Inhibitors

Example Summary

A potent and highly selective inhibitor of protein kinase Cα has been generated via the combinatorial modification of a consensus sequence peptide. The inhibitor displays a K_i of 800 pM versus variable peptide substrate and good selectivity versus other members of the PKC family, including PKCβ (385-fold), PKCγ (580-fold), PKCδ (2730-fold); PKCε (600-fold), PKCη (1310-fold), PKCθ (1210-fold), PKCι (940-fold), and PKCζ (640-fold). The parallel synthesis strategy employed is easily automated and straightforward to implement.

Introduction

We describe herein a library-based strategy that transforms consensus sequences into high affinity ligands in the absence of any tertiary structural information of the protein target. We chose PKCα for our initial studies, an enzyme that is a recognized chemotherapeutic target for several malignant disorders (Nakashima, 2002). The structure of PKCα is not known. A variety of peptide-based inhibitors have been described, the very best of which display IC_{50} or K_i values in the high nM to low μM range, usually using PKC mixtures (Borowski et al., 2000; Ward et al., 1995; Eichholtz et al., 1993; O'Brian and Ward, 1989; Ricouart et al., 1989; Charp et al., 1988; House and Kemp, 1987). The consensus substrate sequence for PKCα is -Arg-Arg-Lys-Gly-Ser-Hyd-Arg- (where Hyd = Phe/Leu/Ile/) (Nishikawa et al., 1997). We designed the closely analogous nonphosphorylatable peptide Ala-Arg-Arg-Gly-Ala-Leu-Arg-Gln-Ala, in which the Ser residue is replaced by Ala. Previous studies have demonstrated that the Arg residues and the hydrophobic amino acid at P-1 promote PKCα recognition (Nishikawa et al., 1997). Consequently, these critical residues were retained and we sought to identify high affinity replacements for presumed nonessential residues or regions on the consensus peptide. In the absence of the 3-dimensional structure of the target protein, three distinct sites on the peptide framework were chosen for the introduction of molecular diversity (libraries **I – III** [FIG. 1]). For example, a peptide containing (L)-2,3-diaminopropionic acid (Dap) at the former Ala position was synthesized, distributed in equal amounts to individual wells of eight 96 well plates, and then acylated with one of 720 different carboxylic acids to create library **II**. Analogous libraries **I** and **III** were constructed as well. Following Dap acylation, the side chain protecting groups were removed with trifluoroacetic acid and the peptide then cleaved from the resin with assay buffer (which contains dithiothreitol). The peptide solutions were filtered into deep well plates, stored, and subsequently evaluated for inhibitory potency using a previously described radioactive assay (See Materials and Methods).

Leads (**1 - 3**) from the three libraries are depicted in FIG. 2. All three compounds display several orders of magnitude improvement in inhibitory efficacy relative to the diacetylated control peptide **4** (Table 1). Interestingly, the best leads from libraries **II** (Coumpound **2**, Table 1) and **III** (Compound **3**) contain the same substituent, a 4-pyrrole phenylacyl moiety. The latter result suggests that PKCα possesses a binding pocket that displays a special affinity for this substituent. Given the weak inhibitory activity displayed by peptide **4**, it is likely that the peptide backbones of **2** and **3** are not rigidly held by the PKCα surface, but rather assume unique enzyme-bound conformations that promote insertion of the 4-pyrrole phenylacyl into a high affinity pocket. Indeed, peptide **5**, which contains the three substituents identified from libraries **I**, **II**, and **III**, displays an inhibitory potency similar to

that of the individual peptide leads **2** and **3**. This result is consistent with the notion that there exists a *single* 4-pyrrole phenylacyl docking site within the substrate-binding region of PKCα. This result also highlights one of the potential pitfalls associated with combining, in a single molecule, lead substituents obtained independently of one another.

Compound	IC_{50} (μM)	K_i (μM)
1	10.4 ± 2.1	not determined
2	5.7 ± 0.4	not determined
3	4.7 ± 0.8	0.55 ± 0.07
4	1100 ± 210	350 ± 80
5	3.1 ± 0.7	not determined
6	0.0019 ± 0.0002	0.00080 ± 0.00025

Table 1. PKCα inhibitory potencies of compounds **1 – 6**. K_i values were obtained by varying peptide substrate concentration.

The ATP binding pocket of PKCα is known to accommodate an array of hydrophobic heterocyclic compounds and could very well serve as the binding site for the pyrrole phenylacyl moiety. We examined this possibility by obtaining the inhibition patterns for peptide **3** (and the diacetylated control peptide **4**). Compound **3** is a competitive inhibitor versus variable peptide substrate (data not shown), but serves as an uncompetitive inhibitor with respect to ATP (FIG. 3). Since ATP and **3** do not act on PKCα in a mutually exclusive fashion, this suggests that the 4-pyrrole phenylacyl moiety binds to a subsite other than the ATP pocket. The advantage associated with this behavior is that the high intracellular levels of ATP will not curtail the inhibitory potency of **3** (Lawrence and Niu, 1998).

The 4-pyrrole phenylacyl group in **3** enhances inhibitory activity by 3 orders of magnitude relative to **4**. Furthermore, peptide **3** surpasses the inhibitory potency displayed by some of the most powerful peptide-based active site-directed inhibitors of PKC, including the 33 amino acid-containing defensins (Charp et al., 1988). Nevertheless, we decided to explore whether an even more potent inhibitor of PKCα could be identified by taking advantage of one of the features inherent within the strategy outlined in FIG. 1. With the acquisition of a lead

substituent at one position in the active site-directed inhibitor (e.g. **3**), it should be possible to employ this substituent as a biasing element in the search for affinity enhancing moieties at other sites on the peptide chain. We chose the 4-pyrrole phenylacyl moiety from peptide **3** as the biasing substituent and prepared sublibrary **IV**, which contains diversity elements positioned at the N-terminus. The primary lead **6** was identified from library **IV** and, as with leads **1 – 3**, resynthesized and enzymologically characterized. Compound **6** displays a K_i of 800 pM, approximately 3 orders of magnitude more potent than compound **3** and 6 orders of magnitude more potent than the starting parent peptide **4**. To the best of our knowledge, compound **6** is the most powerful protein binding site-directed inhibitor ever reported for a protein kinase.

PKCα belongs to a family of closely related protein kinases (PKCs) (Way et al., 2000; Hofmann, 1997). The high sequence homology displayed by the PKC family members has rendered acquisition of isoform-selective inhibitory agents exceedingly difficult (Way et al., 2000; Hofmann, 1997). Indeed, as far as we are aware, a potent PKCα-selective inhibitor has not been reported. Although the leads identified in libraries **I**, **II**, and **III** display a less than 3-fold selectivity for PKCα versus other PKC isoforms (data not shown), extraordinary selectivity is observed with the secondary library lead **6**. The latter exhibits a profound preference for PKCα versus its closely related conventional PKCβ (385-fold) and PKCγ (580-fold) counterparts. Higher selectivities are observed versus the more distantly related novel (PKCδ: 2730-fold; PKCε: 600-fold; PKCη: 1310-fold; PKCθ: 1210-fold) and atypical (PKCι: 940-fold; PKCζ; 640-fold) subfamilies. These results suggest that the N-terminal substituent in **6** accesses a structurally distinct subsite unique to PKCα.

In summary, we have identified an extraordinarily potent and highly selective PKCα inhibitor via the stepwise combinatorial modification of a consensus sequence scaffold. The inhibitory agent exhibits an uncompetitive inhibition versus ATP, thereby suggesting that the intracellular effectiveness of **3** (or **6**) will not be curtailed by the high levels of ATP present in living cells.

Materials and Methods

Materials and Chemicals were obtained from Aldrich, except for piperidine, protected amino acids, 1-hydroxybenzotriazole (HOBt), benzotriazole-1-yloxytris-pyrrolidinophosphonium hexafluorophosphate (PyBOP), N,N,N',N'-tetramethyl-(succinimido)uranium tetrafluoroborate (TSTU), and TentaGel resin, which were obtained from Advanced Chemtech and Bachem. PKC enzymes were purchased from PanVera. Unifilter plates were obtained from Whatman. Solvent-resistant MultiScreen 96-well filter plates and the Multiscreen 96-well filterplate vacuum manifold were purchased from Millipore

Corp.

Peptide Synthesis. All peptides were synthesized on an Advanced Chemtech Model 90 Tabletop Peptide Synthesizer using a standard 9-fluorenylmethoxycarbonyl (Fmoc) solid-phase peptide synthesis protocol. Crude peptides were purified on a preparative HPLC column using three Waters radial compression modules (25 x 10 cm) connected in series. Purified peptides were further characterized by mass spectrometry.

Synthesis of Peptide Libraries I, II and III. TentaGel S COOH (90 μm, 5 g, 0.2 mmol/g) was added to TSTU (5.0 eq, 0.53 g) in 200 mL of DMF and was shaken I h at ambient temperature. Cystamine dihydrochloride (10 eq, 2.25 g) and N-methylmorpholine (NMM; 20 eq, 2.02 g) in 200 mL of H_2O were added to this solution and subsequently shaken overnight at ambient temperature. The free amine substitution level was determined to be 0.025 mmol/g. This low substitution level is ideal for our purposes since this not only ensures a higher coupling yield but, in addition, larger quantities of resin (with greater weight accuracy) can be subsequently introduced into the 96-well plates. The peptide libraries **I**, **II**, and **III** were synthesized on the cystamine-substituted TentaGel resin using a Fmoc solid-phase peptide synthesis protocol. After deprotection of the amino terminal Fmoc (for library **I**) or NH-*t*-butyloxycarbonyl group (tBoc; for libraries **II** and **III**), the resin was extensively washed and subsequently dried *in vacuo*. The peptide–bound resin was distributed in 5-mg quantities into each well of solvent-resistant 96-well filter plates. In addition, each well contained a carboxylic acid-containing compound (400 eq, 20 μmol), PyBOP (200 eq), HOBt (200 eq), and NMM (1,000 eq) in 50 μL of DMF. A total of 720 different carboxylic acids (each dissolved in DMF and added in 100 μL quantities) were employed. The plates were shaken overnight, and then each well subjected to a series of wash steps (3 x 200 μL of DMF, 3 x200 μL of isopropyl alcohol, and 3 x 200 μL of CH_2Cl_2). The NH-4-methoxy-2,3,6-trimethylbenzene-sulfonyl (Mtr) side chain protecting groups were cleaved with trifluoroacetic acid (TFA):thioanisole (95:5) at ambient temperature. The peptide-nonpeptide conjugates were cleaved from the disulfide-containing resin with 10 mM dithiothreitol (DTT) in 50 mM Tris, pH 7.5 (1 x 200 μL for 1 h and 2 x 150 μL for 1 h each) and filtered into a receiving set of 96-well plates using the vacuum manifold (final volume of 500 μL). The efficiency of acid coupling, peptide cleavage from the resin with DTT solution, and purity of peptide-nonpeptide conjugates was assessed via the ninhydrin test and HPLC. No free *N*-terminal peptide was detected, and >90% of total ligand was cleaved from the resin with first the DTT wash step. The final two DTT washings removed the residual resin-bound peptide. Compound purity was >90% as assessed by HPLC, and the HPLC-purified compounds (*i.e.* removal of Tris buffer and DTT) were characterized by matrix-assisted laser desorption ionization mass spectrometry.

Synthesis of Peptide Library IV. The side chain protected peptide resin Fmoc-Ala-Arg-Arg-Gly-Ala-Leu-Arg-Dap-Ala-NH$(CH_2)_2S(CH_2)_2$NH-TentaGel was synthesized as described above for libraries **I** – **III**. The Boc group on the Dap side chain was removed with TFA:CH_2Cl_2 1:1 and subsequently acylated with 4-(1H-pyrol-1-yl)benzoic acid. The N-terminal Fmoc group was removed and the resin-bound peptide distributed in 5 mg quantities into each well of solvent-resistant 96-well filter plates. In addition, each well contained a carboxylic acid-containing compound (400 eq, 20 μmol), PyBOP (200 eq), HOBt (200 eq), and NMM (1,000 eq) in 50 μL of DMF. A total of 720 different carboxylic acids (each dissolved in DMF and added in 100 μL quantities) were employed. The plates were shaken overnight, and then each well subjected to a series of wash steps (3 x 200 μL of DMF, 3 x200 μL of isopropyl alcohol, and 3 x 200 μL of CH_2Cl_2). The Mtr side chains were removed and the peptides cleaved from the resin as described in the protocol for the synthesis of libraries **I** – **III**.

Peptide 3. The peptide was resynthesized using the protocol described above for library **III** with the exception that Arg-Pbf (2,2,4,6,7-pentamethyldihydrobenzofuran-5-sulfonyl) was used in place of Arg-Mtr. The Pbf protecting groups were removed via treatment with TFA:triisopropylsilane (TIS):H_2O (95:2.5:2.5) for 2 – 3 hr. The deprotected peptide was subsequently released from the resin using the DTT cocktail described for library **III**.

^{1}H NMR (D_2O): δ7.96-7.99 (d, J = 8.71 Hz, 2H), 7.74-7.77 (d, J = 8.78 Hz, 2H), 7.48-7.50 (dd, J = 2.20, J = 2.20 Hz, 2H), 6.55-6.57 (dd, J = 2.11 Hz, J = 2.11 Hz, 2H), 4.38-4.42 (m, 8H), 4.01 (s, 2H), 3.94-4.02 (m, 2H), 3.82-3.85 (m, 2H), 3.45 (m, 2H), 3.26-3.31 (m, 4H), 3.15-3.18 (m, 2H), 2.71 (m, 2H), 2.12 (s, 3H), 1.87-1.91 (m, 6H), 1.67-1.73 (m, 8H), 1.44-1.52 (m, 8H), 0.94-0.96 (d, J = 5.97 Hz, 3H), and 0.89-0.91 (d, J = 5.97 Hz, 3H); ESIMS *m/z* calculated for $C_{53}H_{87}N_{21}O_{11}S$ 1226.6, 1227.6, 1228.6 (MH^+), Found *m/z* 1226.6, 1227.5, 1228.4.

Peptide 4. The side chain protected peptide resin Fmoc-Ala-Arg-Arg-Gly-Ala-Leu-Arg-Dap-Ala-NH-Rink resin was synthesized using the protocol described above for library **III** using Rink SS resin instead of TentaGel S COOH. The deprotected peptide was subsequently released from the resin using a TFA/TMSBr/ethanedithiol/m-cresol/thioanisole cocktail (v/v 70:13:5:1:11) for 15 min under a blanket of N_2 at 0 °C.

ESIMS *m/z* calculated for $C_{43}H_{79}N_{19}O_{11}$ 1038.6, 1039.6, 1040.6 (MH^+), Found *m/z* 1038.9, 1039.9, 1040.9.

Peptide 6. The peptide was resynthesized using the protocol described above for library **IV** with the exception that Arg-Pbf was used in place of Arg-Mtr. The Pbf protecting groups were removed via treatment with TFA:TIS:H_2O (95:2.5:2.5) for 2 – 3 hr. The

deprotected peptide was subsequently released from the resin using the DTT cocktail described for library **IV**.

^{1}H NMR (D_2O): δ7.95 (d, J = 8.74 Hz, 2H), 7.70-7.78 (m, 3H), 7.53-7.60 (m, 4H), 7.44-7.49 (m, 2H), 6.79 (d, J = 8.74 Hz, 1H), 4.38-4.42 (m, 8H), 3.67-3.98 (m, 29H), 3.42-3.49 (m, 3H), 3.09-3.40 (m, 6H), 2.65-2.72 (m, 2H), 1.47-1.91 (m, 24H), 0.89-0.98 (m, 6H); ESIMS calculated for $C_{59}H_{89}N_{21}O_{11}SCl_2$ *m/z* 1370.6, 1371.6, 1372.6, 1373.6, 1374.6, 1375.6, 1376.6 (MH^+), Found *m/z* 1370.8, 1371.8, 1372.8, 1373.7, 1374.8, 1375.9, 1376.7.

Protein Kinase C Assay (general). The peptides Ac-Ser-Phe-Arg-Arg-Arg-NH_2 (for PKC α, β and γ) and acetyl-Pro-Arg-Lys-Arg-Glu-Gly-Ser-Val-Arg-Arg-Arg-NH_2 (for PKC ε and ζ) were used as substrates. The K_m values for these peptides are 15 μM (PKCα) and 5.9 μM (PKCε), respectively, whereas the V_{max} values are 0.526 μmol/min-mg (PKCα) and 1.445 μmol/min-mg (PKCε), respectively.

Protein Kinase Cα Assay (library screening). 20 μL of 37.5 μM peptide inhibitor candidate (from each well of libraries **I**, **II**, **III**, and **IV**) was added to each well of 96 multiwell assay plates containing 20 μL assay buffer [62.5 mM HEPES (pH 7.5), 50 μM Ac-Ser-Phe-Arg-Arg-Arg-NH_2, 2.0 mM $CaCl_2{\cdot}2H_2O$, 34 mM $MgCl_2{\cdot}6H_2O$, 1.4 mM EGTA·Na, phosphatidylserine (225 μg/mL), diacylglycerol (40 μg/mL) and 313 μM cold ATP supplemented with 70 - 163 μCi/well [γ-^{33}P]ATP for radioactive detection]. 10 μL enzyme diluted buffer containing 20 mM Tris (pH 7.5), PKC (0.5 ng/μL), 1 mM DTT, BSA (730 μg/mL) and 1 mM EDTA·4Na·$2H_2O$ were added last to initiate the reaction. Total reaction volume was 50 μL. After a 10-min incubation at 30 °C, 100 μL of 6% phosphoric acid was added to each well to stop the reaction (total volume: 150 μL). Following an additional 5 min incubation at ambient temperature, 75 μL from each reaction well was transferred into each well of a Unifilter (P81 cellulose phosphate paper) assay plate and washed four times with 0.1% phosphoric acid in water. Scintillation solution was added to each well and ^{33}P-incorporation measured by scintillation counting with a MicroBeta™ TriLux & MicroBeta JET (Perkin Elmer). IC_{50} values were calculated using GraFit (Erithacus Software Limited) and K_i values were calculated using Enzyme Kinetics, SigmaPlot (SPSS Inc.)

PKCε and ζ Assay (IC_{50} determinations). 20 μL of 37.5 μM peptide library was added in 20 μL assay buffer containing 62.5 mM HEPES (pH 7.5), 1 M $MgCl_2{\cdot}6H_2O$, 40 mM EGTA·Na, PS (10 mg/mL) and 295 μM cold ATP supplemented with 70 - 163 μCi/well [γ-^{33}P]ATP for radioactive detection. 10 μL enzyme diluted buffer containing 10 mM HEPES (pH 7.5), 10 mM DTT, BSA(3.8 mg/mL), 10 mM EDTA·4Na·$2H_2O$ and PKC (20 ng/μL) were added last to this buffer. Reactions were carried out as described above for the Protein Kinase Cα assay.

Protein Kinase Cα Assay (K_i determination for peptides 3 and 4 versus variable Ac-Ser-Phe-Arg-Arg-Arg-NH_2 substrate). 20 μL of peptide **3** (concentrations = 0, 1.25, 2.5, 5 and 10 μM) was added to a 20 μL assay buffer containing 62.5 mM HEPES (pH 7.5), peptide substrate (concentrations = 10, 20, 40 and 80 μM), 2.0 mM $CaCl_2 \cdot 2H_2O$, 34 mM $MgCl_2 \cdot 6H_2O$, 1.4 mM EGTA·Na, phosphatidylserine (225 μg/mL), diacylglycerol (40 μg/mL), and 313 μM cold ATP supplemented with 70-163 μCi/well [γ^{33}P]ATP for radioactive detection. 10 μL enzyme diluted buffer containing 20 mM Tris (pH 7.5), PKC (0.5 ng/μL), 1 mM DTT, BSA (730 μg/mL) and 1 mM EDTA·4Na·$2H_2O$ were added to initiate the reaction. Subsequent assay workup and scintillation counting were performed as described under "Protein Kinase C α, β and γ Assay (library screening)". An analogous protocol was employed for peptide **4** versus variable [Ac-Ser-Phe-Arg-Arg-Arg-NH_2].

Protein Kinase Cα Assay (K_i determination for peptides 3 and 4 versus variable ATP). 20 μL of peptide **3** (concentrations = 0, 1.25, 2.5, 5 and 10 μM) was added to a 20 μL assay buffer containing 62.5 mM HEPES (pH 7.5), 50 μM peptide substrate, 2.0 mM $CaCl_2 \cdot 2H_2O$, 34 mM $MgCl_2 \cdot 6H_2O$, 1.4 mM EGTA·Na, phosphatidylserine (225 μg/mL), diacylglycerol (40 μg/mL), and cold ATP (concentrations = 10, 12.5, 16.5, 25 and 50 μM each) supplemented with 7-16 μCi/well [γ^{33}P]ATP for radioactive detection. 10 μL enzyme diluted buffer containing 20 mM Tris (pH 7.5), PKC (0.5 ng/μL), 1 mM DTT, BSA (730 μg/mL) and 1 mM EDTA·4Na·$2H_2O$ were added to initiate the reaction. Subsequent assay workup and scintillation counting were performed as described under "Protein Kinase C α, β and γ Assay (library screening)". An analogous protocol was employed for peptide **4** versus variable [ATP].

Protein Kinase Cα Assay (K_i determination for peptide 6 versus variable Ac-Ser-Phe-Arg-Arg-Arg-NH_2 substrate). The assay was conducted as described above for peptide **3** versus variable peptide substrate with the exception that the enzyme solution contained a ten-fold lower concentration of PKCα (0.05 ng/μL). The reaction was initiated as described above. After an 18-min incubation at 30 °C, 100 μL of 6% phosphoric acid was added to each well to stop the reaction (total volume: 150 μL). Following an additional 5 min incubation at ambient temperature, 75 μL from each reaction well was transferred into each well of a Unifilter (P81 cellulose phosphate paper) assay plate and washed four times with 0.1% phosphoric acid in water. Scintillation solution was added to each well and ^{33}P-incorporation measured by scintillation counting with a MicroBeta™ TriLux & MicroBeta JET (Perkin Elmer). IC_{50} values were calculated using GraFit (Erithacus Software Limited) and K_i values were calculated using Enzyme Kinetics, SigmaPlot (SPSS Inc.)

Protein Kinase Cα Assay (IC_{50} determination for peptide 6 versus histone III-S substrate). 20 μL assay buffer solution containing 62.5 mM Hepes (pH 7.5), $CaCl_2.2H_2O$ (1.88 mM), $MgCl_2.6H_2O$ (31.3 mM), EGTA.Na (1.3 mM), PS (450 μg/mL), DAG 40 μg/mL, cold ATP (313 μM), supplemented with 70-163 μCi/well [^{33}P]ATP for radioactive detection with 625 nM histone III-S as substrate were added to 20 μL of a solution containing peptide **6** at various concentrations (4, 8, 16, 32, 64, 128, 256, 512 nM). 10 μL enzyme buffer solution containing 20 mM Tris (pH 7.5), PKCα (0.05 ng/μL), 1 mM DTT, BSA (730 μg/ mL), and EDTA.4Na.$2H_2O$ (1 mM) were added to start the reaction. After an 18 min incubation at 30 °C, 100 μL of 6% phosphoric acid was added to quench the reaction at room temperature. The resulting volume in each individual well is 150 μL. Following an additional 5 min incubation, 75 μL from each well was transferred to Unifilter P81 cellulose phosphate paper and washed with 0.1% phosphoric acid (3 x 200 μL) and water (200 μL). Scintillation solution was added to each well and ^{33}P incorporation measured by scintillation counting with MicroBeta™ TriLux & MicroBeta JET (Perkin Elmer). The IC_{50} value for compound **6** as an inhibitor of histone III-S phosphorylation was found to be 31.7 ± 0.8 nM as calculated using GraFit (Erithacus Software Limited).

Fluorescein-labeled Peptide 7. Peptide **3** (3.67 mg, 3.0 mmol) and 5-iodoacetamidofluorescein (3.09 mg, 6.0 mmol) were added to 2 mL of Tris buffer (100 mM, pH 7.5) and subsequently shaken overnight at ambient temperature in the dark. ^{1}H NMR (D_2O); δ7.96 (s, 1H), 7.61-7.52 (m, 3H), 7.18-7.16 (m, 2H), 7.00 (s, 1.5H), 6.75-6.54 (m, 8H), 6.20 (s, 1.5H), 4.23-4.11 (m, 6H), 3.80 (m, 2H), 3.65 (s, 2H), 3.54-3.51 (m, 4H), 3.50-3.41 (m, 4H), 3.04-2.93 (m, 6H), 2.76-2.72 (m, 2H), 1.92 (s, 3H), 1.69-1.65 (m, 5H), 1.47-1.43 (m, 8H), 1.26-1.09 (m, 9H), and 0.62-0.65 (m, 6H); ESIMS *m/z* calculated for $C_{75}H_{100}N_{22}O_{17}S$ 1612.7, 1613.7, 1614.7 (MH^+), Found *m/z* 1612.5, 1613.5, 1614.5

Determination of K_D Values. The K_D value for the fluorescein-labeled peptide **7**/PKCα complex was determined via equilibrium dialysis (note: peptide **7** does not exhibit any significant change in fluorescence upon binding to PKCα). All samples were prepared in a buffer containing 50 mM HEPES (pH 7.5), 0.8 mM $CaCl_2.2H_2O$, 13.6 mM $MgCl_2.6H_2O$, 0.56 mM EGTA Na, phosphatidylserine (90 μg/mL), diacylglycerol (16 μg/mL), 4 mM Tris (pH 7.5), 0.2 mM DTT, BSA (146 μg/mL), 0.2 mM EDTA.4Na.$2H_2O$ and AMP-PNP (a nonhydrolyzable ATP analogue) or without AMP-PNP at pH 7.5. Slide-A-Lyzer dialysis slide cassettes (Pierce, 10K MWCO, 0.1 - 0.5 mL capacity) were employed and contained 250 nM PKCα and 500 nM fluorescein-labeled peptide **7**. The slide cassettes contained a final volume of 180 μL. The cassettes were placed in beaker containing a volume of buffer solution that was at least 500-fold greater than that of the sample volume in the dialysis slide cassette.

Equilibrium dialysis experiments were performed over a period of 16 hr and maintained at 4 °C. The fluorescence intensity of the solutions in the slide cassette (F_i) and in the beaker (F_o) was measured. The excitation wavelength for the fluorescein-labeled peptide **7** was 499 nm and the emission monitored at 519 nm. The K_D values were calculated from Equation 1. K_D = 203 nM (with AMP-PNP) and 1.8 μM (without AMP-PNP).

$$E_D = \frac{\{[E]_T - [E \bullet P]\}[P]}{[E \bullet P]}$$

where $[E]_T$ = total enzyme concentration; [E•P] = enzyme-peptide complex; [P] = free peptide concentration.

Example 2. Inhibitors of PKCδ and PKCζ.

Using the consensus sequence Arg-Arg-Gln-Gly-Dap-Phe-Met-Tyr-Phe, a library of 720 compounds, each conjugated with a different carboxylic acid at the Dap moiety, were prepared and tested for inhibitory activity against PKCδ and PKCζ. The lead compound that was the most inhibitory of these for both PKCδ and PKCζ was used to construct two additional libraries. The first library comprised 720 different carboxylic acids at the N-terminal nitrogen. None of the compounds in that library improved the selectivity or inhibitory activity of the original lead compound. Another library was therefore constructed, which had 54 compounds, each compound conjugated with a different aldehyde at the N-terminal nitrogen. Since, under physiological conditions, the aldehyde at the alkylated terminal amine of the consensus sequence would have a positive charge as opposed to the carboxylic acid's amide neutral charge, we reasoned that the aldehyde library could provide improved specificity and inhibitory activity where the carboxylic acid library could not.

PKC Isoforms		ζ inhibitor	Selectivity	δ inhibitor	Selectivity
Conventional	α	>40 μM	>5300	17 μM	940
	β	5.5 μM	730	2.2 μM	125
	γ	>40 μM	>5300	7.0 μM	390
Novel	δ	4.5 μM	600	**18 nM**	**1**
	ε	35 μM	4600	12 μM	667
	θ	19 μM	2530	15 μM	830
	η	18 μM	2400	22 μM	1220
Atypical	ζ	**7.5 nM**	**1**	3.5 μM	194
	ι	14 μM	1860	450 nM	25

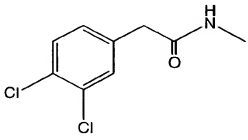
In view of the above, it will be seen that the several advantages of the invention are achieved and other advantages attained.

As various changes could be made in the above methods and compositions without departing from the scope of the invention, it is intended that all matter contained in the above description and shown in the accompanying drawings shall be interpreted as illustrative and not in a limiting sense.

All references cited in this specification are hereby incorporated by reference. The discussion of the references herein is intended merely to summarize the assertions made by the authors and no admission is made that any reference constitutes prior art. Applicants reserve the right to challenge the accuracy and pertinence of the cited references.

What is claimed is:

1. An inhibitor of a protein kinase Cα (PKCα), the inhibitor comprising A-Ala-Arg-Arg-X-B-Hyd-C-D-, where A =AcHN-,



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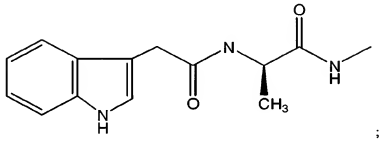
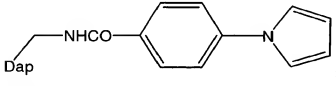


;

X=any amino acid or amino acid mimetic; B=Ala or a diaminopropionic acid (Dap) derivative having the formula



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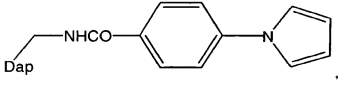
Hyd=Phe, Leu or Ile; C=Arg or Lys; and D=Ala or a Dap derivative having the formula



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wherein any of the amino acids can alternatively be an analogous amino acid mimetic.

2. The inhibitor of claim 1, having an IC_{50}<50 μM for the PKCα.

3. The inhibitor of claim 1, having an IC_{50}<10 μM for the PKCα.

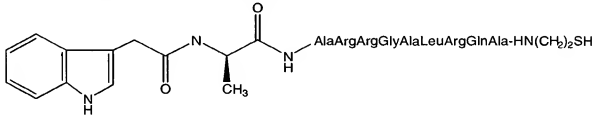
4. The inhibitor of claim 1, having an IC_{50}<1 μM for the PKCα.

5. The inhibitor of claim 1, wherein the inhibitor has an IC_{50} for the PKCα <0.1 that of any other PKC isoform.

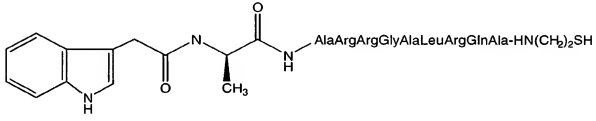
6. The inhibitor of claim 1, wherein the inhibitor has an IC_{50} for the PKCα <0.01 that of any other PKC isoform.

7. The inhibitor of claim 1, wherein the PKCα is a human PKCα.

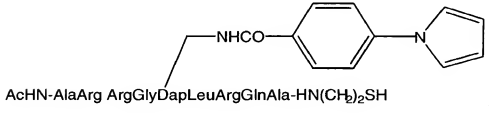
8. The inhibitor of claim 1, comprising



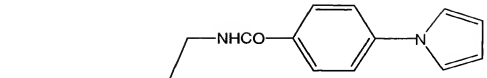
9. The inhibitor of claim 1, consisting of



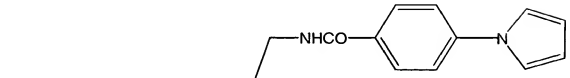
10. The inhibitor of claim 1, comprising



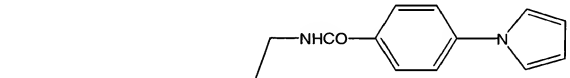
11. The inhibitor of claim 1, consisting of



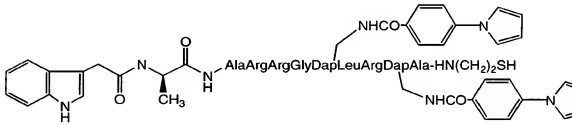
12. The inhibitor of claim 1, comprising



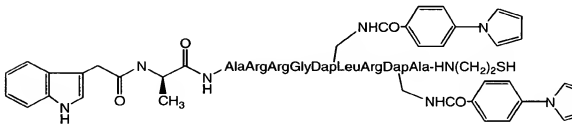
13. The inhibitor of claim 1, consisting of



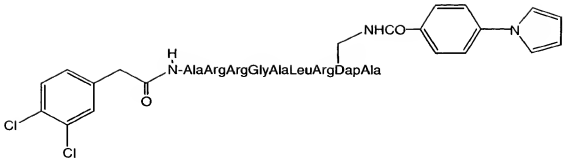
14. The inhibitor of claim 1, comprising



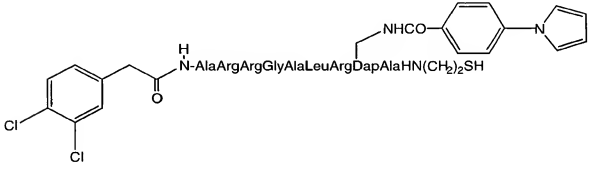
15. The inhibitor of claim 1, consisting of



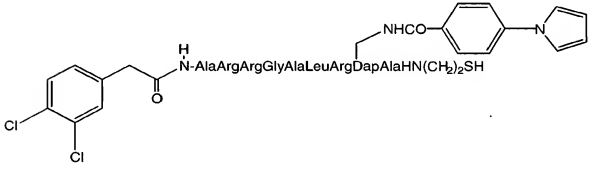
16. The inhibitor of claim 1, comprising



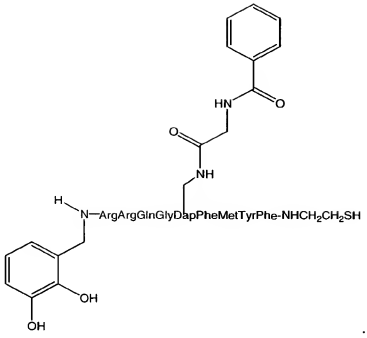
17. The inhibitor of claim 1, comprising



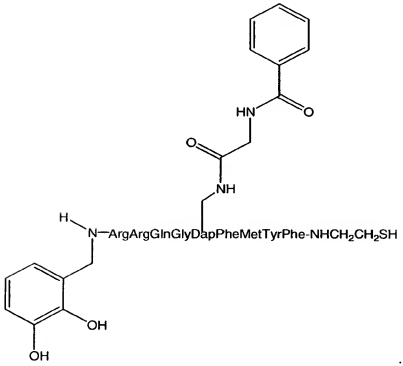
18. The inhibitor of claim 1, consisting of



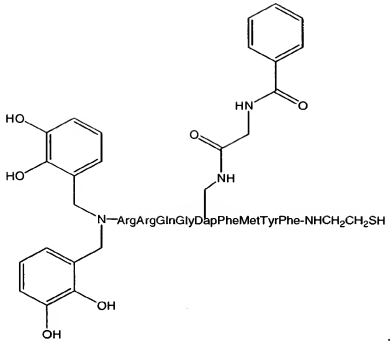
19. An inhibitor of a protein kinase Cδ (PKCδ), the inhibitor comprising



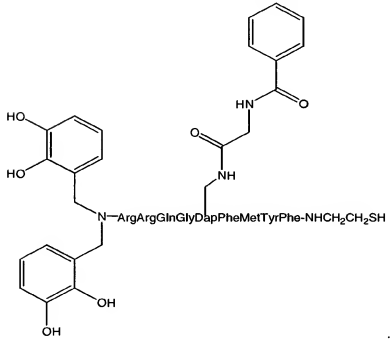
20. The inhibitor of claim 19, the inhibitor consisting of



21. An inhibitor of a protein kinase Cζ (PKCζ), the inhibitor comprising



22. The inhibitor of claim 21, consisting of



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23. A composition comprising the inhibitor of any one of claims 1-22 in a pharmaceutically acceptable excipient.

24. A combinatorial library useful for identifying an inhibitor of a protein kinase, the combinatorial library comprising a plurality of compounds, each compound comprising

a consensus sequence for a substrate of the protein kinase, the consensus sequence comprising at least five amino acids or mimetics, wherein at least one amino acid or mimetic is not essential to substrate binding, and wherein an amino acid or mimetic not subject to phosphorylation substitutes a canonical Ser or Thr target residue in the consensus sequence; and

a chemical moiety covalently bound to the compound at

the at least one non-essential amino acid or mimetic in the consensus sequence and/or

the amino acid or mimetic not subject to phosphorylation substituting the canonical Ser or Thr target residue;

wherein each compound comprises a different chemical moiety.

25. The combinatorial library of claim 24, wherein the non-essential amino acid or mimetic and/or the amino acid or mimetic substituting a canonical Ser or Thr target residue is a diaminopropionic acid (Dap).

26. The combinatorial library of claim 24, wherein the chemical moiety on each compound is a carboxylic acid.

27. The combinatorial library of claim 26, wherein the carboxylic acid on each compound is selected from any one of the carboxylic acid moieties provided in FIG. 4.

28. The combinatorial library of claim 24, wherein the chemical moiety on each compound is an aldehyde.

29. The combinatorial library of claim 28, wherein the aldehyde is selected from any one of the aldehyde moieties provided in FIG. 5.

30. The combinatorial library of claim 24, wherein the chemical moiety is covalently bound to a diaminopropionic acid (Dap).

31. The combinatorial library of claim 24, wherein the chemical moiety is covalently bound to the residue not subject to phosphorylation substituting the canonical Ser or Thr target residue.

32. The combinatorial library of claim 24, wherein the substitute residue is Ala.

33. The combinatorial library of claim 24, wherein the protein kinase is a mammalian protein kinase.

34. The combinatorial library of claim 24, wherein the protein kinase is a human protein kinase.

35. The combinatorial library of claim 24, wherein the protein kinase is a protein kinase C (PKC).

36. The combinatorial library of claim 35, wherein the PKC is a PKCα.

37. The combinatorial library of claim 36, wherein the consensus sequence for a substrate of the PKCα comprises LysGlySerHyd(Arg/Lys), where Hyd is Phe, Leu or Ile.

38. The combinatorial library of claim 32, wherein the protein kinase is a PKCα and the consensus sequence with the substituted Ala residue is AlaArgArgGlyAlaLeuArgGlnAla.

39. The combinatorial library of claim 24, wherein the protein kinase is a PKCβI and the consensus sequence comprises ArgLysGlySerPheLys.

40. The combinatorial library of claim 24, wherein the protein kinase is a PKCβII and the consensus sequence comprises ArgLysGlySerPheLys.

41. The combinatorial library of claim 24, wherein the protein kinase is a PKCγ and the consensus sequence comprises ArgLysGlySerPheLys.

42. The combinatorial library of claim 24, wherein the protein kinase is a PKCδ and the consensus sequence comprises (Lys/Gln)GlySerPhe(Phe/Met).

43. The combinatorial library of claim 24, wherein the protein kinase is a PKCε and the consensus sequence is Lys(Met/Lys)Ser(Phe/Ala)(Glu/Tyr/Asp/Phe).

44. The combinatorial library of claim 24, wherein the protein kinase is a PKCη and the consensus sequence is ArgArgSerPheArgArg.

45. The combinatorial library of claim 24, wherein the protein kinase is a PKCζ and the consensus sequence is (Arg/Gln/Lys/Glu)(Met/Gly)Ser(Phe/Met)(Phe/Met).

46. The combinatorial library of claim 24, wherein the protein kinase is a PKCμ and the consensus sequence is (Gln/Lys/Glu/Met)MetSer(Val/Met/Leu)(Ala/Met/Val).

47. The combinatorial library of claim 24, comprising at least 10 compounds.

48. The combinatorial library of claim 24, comprising at least 100 compounds.

49. A method of identifying an inhibitor of a protein kinase, the method comprising

creating the combinatorial library of claim 24, for the protein kinase,

screening the compounds in the combinatorial library for inhibitory activity of the protein kinase, and

identifying any compounds in the combinatorial library that are inhibitors of the protein kinase.

50. The method of claim 49, further comprising creating another combinatorial library from an inhibitor identified in the identifying step.

51. The method of claim 49, wherein each compound is screened separately for inhibitory activity.

52. The method of claim 49, wherein more than one compound is screened together for inhibitory activity.

53. The method of claim 49, wherein the protein kinase is a mammalian protein kinase.

54. The method of claim 49, wherein the protein kinase is a human protein kinase.

55. The method of claim 49, wherein the protein kinase is a protein kinase C (PKC).

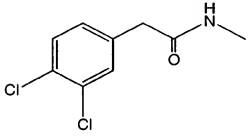
56. The method of claim 55, wherein the PKC is a PKCα, a PKCδ, or a PKCζ.

57. A method of treating a deleterious condition in a mammal, where the condition is dependent on a protein kinase for induction or severity, the method comprising contacting the mammal with an inhibitor of the protein kinase found by the method of claim 49.

58. The method of claim 57, wherein the protein kinase is a protein kinase C (PKC).

59. The method of claim 58, wherein the PKC is a PKCα.

60. The method of claim 59, wherein the inhibitor comprises A-Ala-Arg-Arg-X-B-Hyd-C-D-, where A- =AcHN-,



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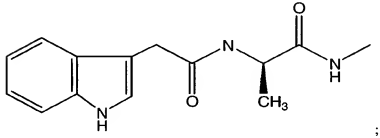

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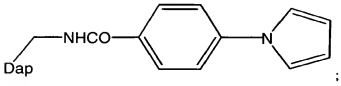
X=any amino acid or amino acid mimetic; B=Ala or a diaminopropionic acid (Dap) derivative having the formula



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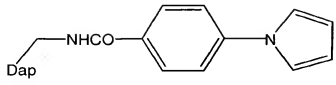
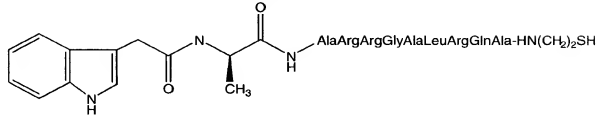
Hyd=Phe, Leu or Ile; C=Arg or Lys; and D=Ala or a Dap derivative having the formula



wherein any of the amino acids can alternatively be an analogous amino acid mimetic.

61. The inhibitor of claim 59, selected from the group consisting of



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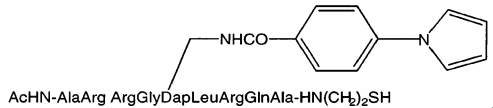

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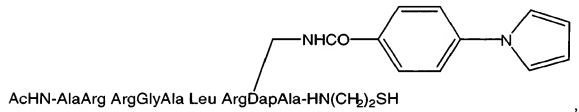

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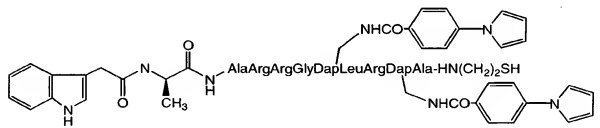

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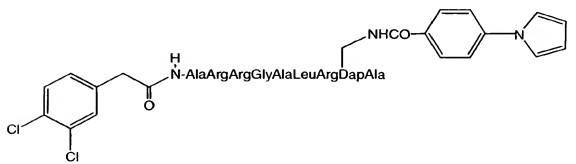
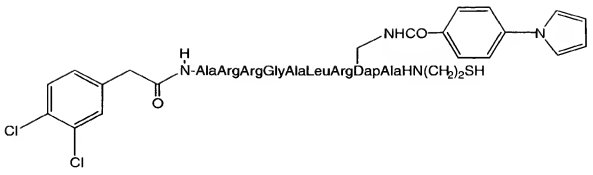
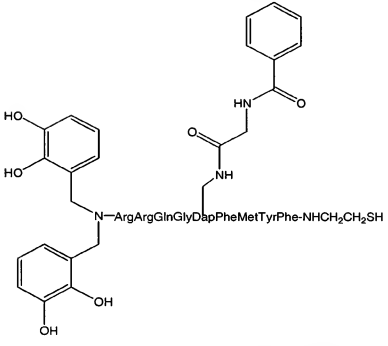


and



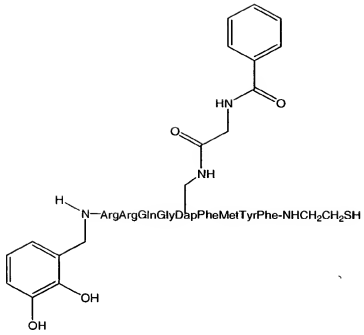
62. The method of claim 58, wherein the PKC is a PKCδ.

63. The method of claim 52, wherein the inhibitor is



64. The method of claim 58, wherein the PKC is a PKCζ.

65. The method of claim 64, wherein the inhibitor is



66. The method of claim 57, wherein the deleterious condition is selected from the group consisting of a cancer, a cardiovascular disease, type 2 diabetes, agammaglobulinaemia, reperfusion injury, Alzheimer's disease, a neurological or neurodegenerative disease, chemotherapy-induced alopecia, arthritis, an autoimmune disease, an inflammatory disease, allergies, asthma and viral virulence.

67. The method of claim 57, wherein the deleterious condition is cancer.

68. The method of claim 57, wherein the deleterious condition is heart disease.

69. The method of claim 57, wherein the deleterious condition is type 2 diabetes and the protein kinase is a PKCδ.

70. The method of claim 57, wherein the mammal is a human.

71. A method of inhibiting a protein kinase, the method comprising contacting the protein kinase with an inhibitor of the protein kinase identified by the method of claim 49.

72. The method of claim 71, wherein the protein kinase is a mammalian protein kinase.

73. The method of claim 71, wherein the protein kinase is in a living mammalian cell.

74. The method of claim 73, wherein the cell is in a living mammal.

75. The method of claim 74, wherein the living mammal is a human.

76. The method of claim 74, wherein the mammal has deleterious condition that is dependent on the protein kinase for induction or severity.

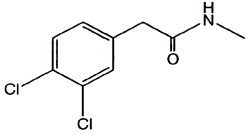
77. The method of claim 76, wherein the deleterious condition is selected from the group consisting of a cancer, a cardiovascular disease, type 2 diabetes, agammaglobulinaemia, reperfusion injury, Alzheimer's disease, a neurological or neurodegenerative disease, chemotherapy-induced alopecia, arthritis, an autoimmune disease, an inflammatory disease, allergies, asthma and viral virulence.

78. The method of claim 76, wherein the deleterious condition is a cancer.

79. The method of claim 73, wherein the protein kinase is a protein kinase C (PKC).

80. The method of claim 79, wherein the PKC is a PKCα.

81. The method of claim 80, wherein the inhibitor comprises A-Ala-Arg-Arg-X-B-Hyd-C-D-, where A- =AcHN-,



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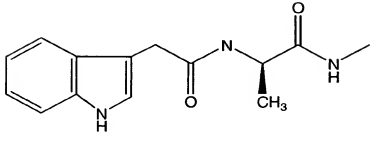

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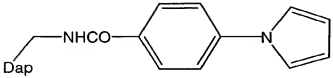
X=any amino acid or amino acid mimetic; B=Ala or a diaminopropionic acid (Dap) derivative having the formula



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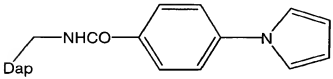
Hyd=Phe, Leu or Ile; C=Arg or Lys; and D=Ala or a Dap derivative having the formula



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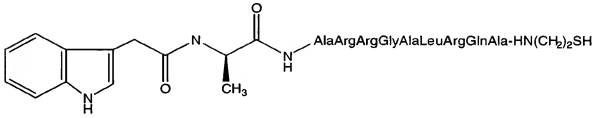
wherein any of the amino acids can alternatively be an analogous amino acid mimetic.

82. The method of claim 80, wherein the inhibitor is selected from the group consisting of



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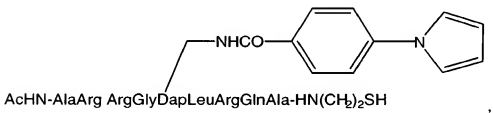

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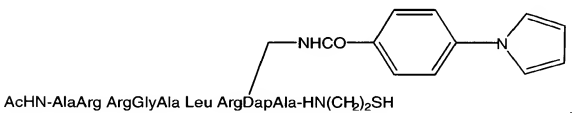

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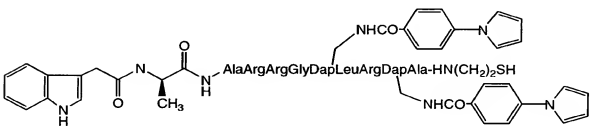

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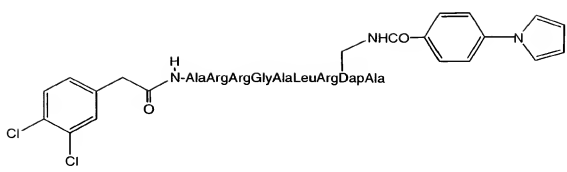
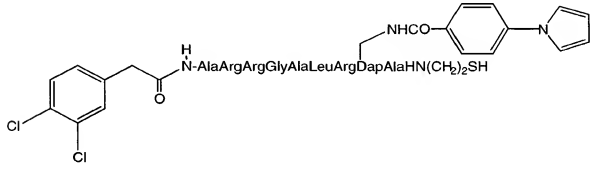
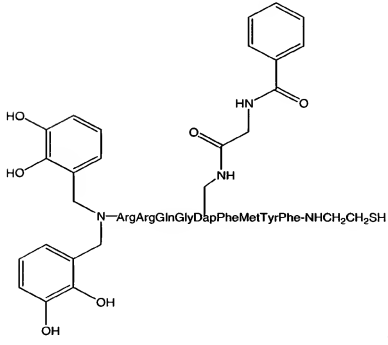


and



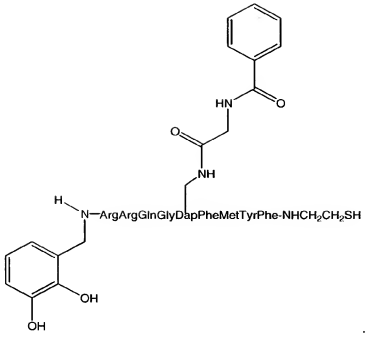
83. The method of claim 79, wherein the PKC is a PKCδ.

84. The method of claim 83, wherein the inhibitor is



85. The method of claim 79, wherein the PKC is a PKCζ.

86. The method of claim 85, wherein the inhibitor is



87. Use of an inhibitor of a protein kinase in the manufacture of a medicament for the treatment of a deleterious condition in a mammal that is dependent on a protein kinase for induction or severity, the treatment comprising contacting the mammal with an inhibitor of the protein kinase found by the method of claim 49.

Abstract

Inhibitors of protein kinase C (PKC)α, PKCδ and PKCζ are provided which are selective for those PKC isotypes. Combinatorial libraries for identifying protein kinases are also provided, as are methods of identifying protein kinases using those libraries. Additionally, methods of treating a mammal having a deleterious condition, where the condition is dependent on a protein kinase for induction or severity, are provided. Methods of inhibiting protein kinases are also provided.

FIG. 1

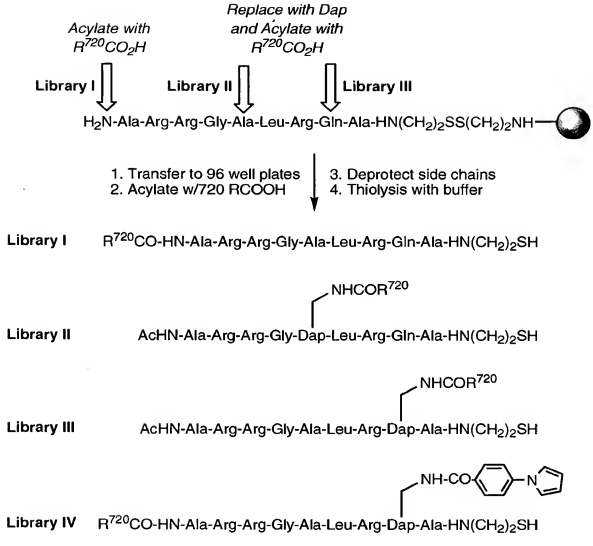

Acylate with $R^{720}CO_2H$
Replace with Dap and Acylate with $R^{720}CO_2H$
Library I
Library II
Library III
H_2N-Ala-Arg-Arg-Gly-Ala-Leu-Arg-Gln-Ala-HN$(CH_2)_2SS(CH_2)_2$NH
1. Transfer to 96 well plates
2. Acylate w/720 RCOOH
3. Deprotect side chains
4. Thiolysis with buffer
Library I
R^{720}CO-HN-Ala-Arg-Arg-Gly-Ala-Leu-Arg-Gln-Ala-HN$(CH_2)_2$SH
Library II
NHCOR^{720}
AcHN-Ala-Arg-Arg-Gly-Dap-Leu-Arg-Gln-Ala-HN$(CH_2)_2$SH
Library III
NHCOR^{720}
AcHN-Ala-Arg-Arg-Gly-Ala-Leu-Arg-Dap-Ala-HN$(CH_2)_2$SH
Library IV
NH-CO
N
R^{720}CO-HN-Ala-Arg-Arg-Gly-Ala-Leu-Arg-Dap-Ala-HN$(CH_2)_2$SH

FIG. 2

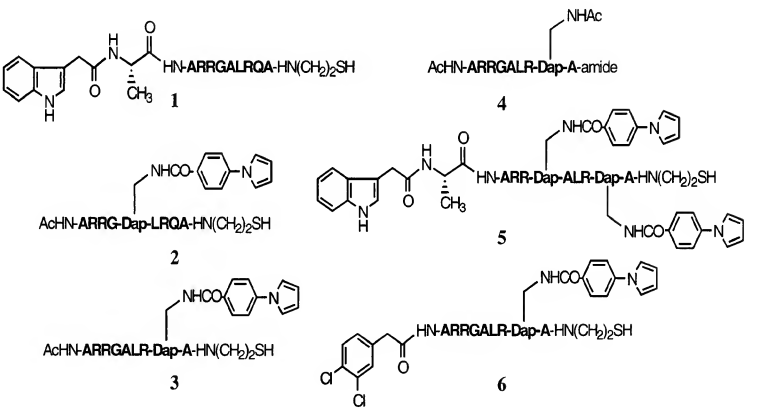
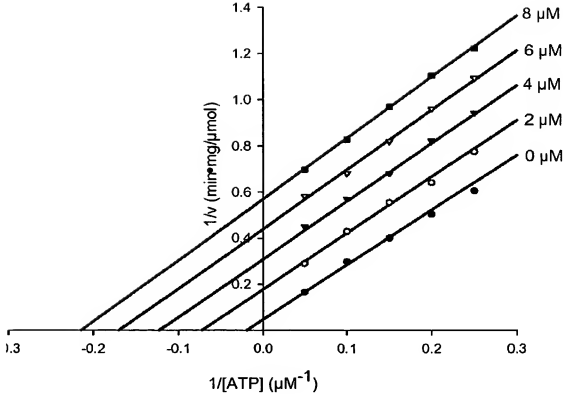

HN-ARRGALRQA-HN(CH2)2SH
1
AcHN-ARRG-Dap-LRQA-HN(CH2)2SH
2
AcHN-ARRGALR-Dap-A-HN(CH2)2SH
3
AcHN-ARRGALR-Dap-A-amide
4
HN-ARR-Dap-ALR-Dap-A-HN(CH2)2SH
5
HN-ARRGALR-Dap-A-HN(CH2)2SH
6
NHAc
NHCO
Cl

FIG. 3


1.4
1.2
1.0
0.8
0.6
0.4
0.2
1/v (min•mg/μmol)
8 μM
6 μM
4 μM
2 μM
0 μM
-0.3
-0.2
-0.1
0.0
0.1
0.2
0.3
1/[ATP] (μM-1)

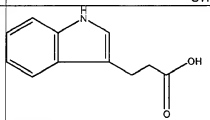
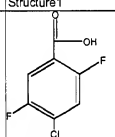
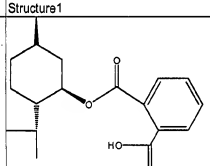
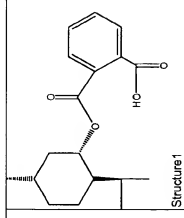
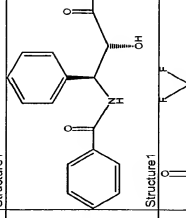
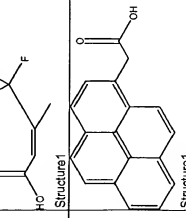
#	STRUCTURE	PRODNAME
1	 Structure1	3-INDOLEPROPIONIC ACID
2	 Structure1	4-CHLORO-2,5-DIFLUOROBENZOIC ACID
3	 Structure1	MONO-(1R)-(-)-MENTHYL PHTHALATE

FIG. 4-A

FIG. 4-B

4	 Structure1	MONO-(1S)-(+)-MENTHYL PHTHALATE
5	 Structure1	N-BENZOYL-(2R,3S)-3-PHENYLISOSERINE
6	 Structure1	4,4,4-TRIFLUORO-3-METHYL-2-BUTENOIC ACID
7	Structure1	1-PYRENEACETIC ACID

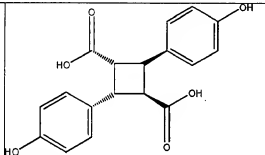
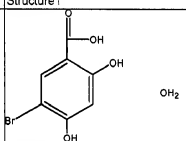
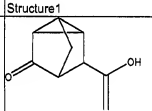
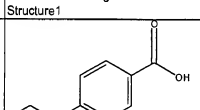
8	 Structure1	(1ALPHA,2ALPHA,3BETA,4BETA)-2,4-BIS(4-HYDROXYPHE
9	 Structure1	5-BROMO-2,4-DIHYDROXYBENZOIC ACID MONOHYDRAT
10	 Structure1	ANTI-3-OXOTRICYCLO(2.2.1.02,6)HEPTANE-7-CARBOXYL
11	 Structure1	4-(ETHYLTHIO)BENZOIC ACID

FIG. 4-C

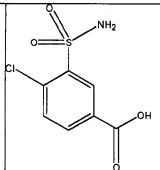
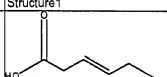
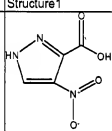
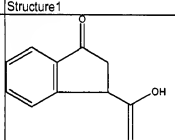
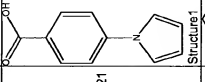
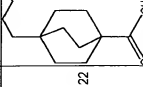
12	 Structure1	4-CHLORO-3-SULFAMOYLBENZOIC ACID
13	 Structure1	TRANS-3-HEXENOIC ACID
14	 Structure1	4-NITRO-3-PYRAZOLECARBOXYLIC ACID
15	 Structure1	3-OXO-1-INDANCARBOXYLIC ACID

FIG. 4-D

FIG. 4-E

16	 Structure1	D-3-PHENYLLACTIC ACID
17	Structure1	3,5-DIBROMOBENZOIC ACID
18	Structure1	2-(TRIFLUOROMETHYL)ACRYLIC ACID
19	Structure1	2-METHOXY-4-NITROBENZOIC ACID

FIG. 4-F

20	 Structure1	3-CHLORO-4-FLUOROBENZOIC ACID
21	 Structure1	4-(1H-PYRROL-1-YL)BENZOIC ACID
22	 Structure1	4-PENTYLBICYCLO(2.2.2)OCTANE-1-CARBOXYLIC ACID

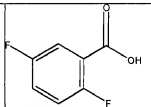
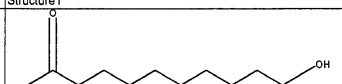
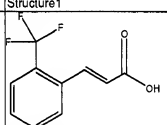
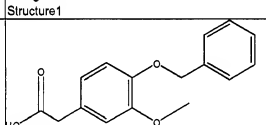
23	 Structure1	2,5-DIFLUOROBENZOIC ACID
24	 Structure1	10-HYDROXYDECANOIC ACID
25	 Structure1	2-(TRIFLUOROMETHYL)CINNAMIC ACID
26	 Structure1	4-BENZYLOXY-3-METHOXYPHENYLACETIC ACID

FIG. 4-G

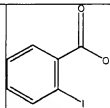
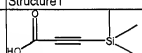
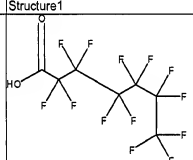
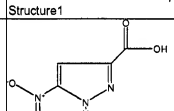
27	 Structure1	2-IODOBENZOIC ACID
28	 Structure1	3-(TRIMETHYLSILYL)PROPYNOIC ACID
29	 Structure1	TRIDECAFLUOROHEPTANOIC ACID
30	 Structure1	5-NITRO-3-PYRAZOLECARBOXYLIC ACID

FIG. 4-H

FIG. 4-I

31	Structure1	2-BROMO-4,5-DIMETHOXYBENZOIC ACID
32	Structure1	TRANS-2-CHLORO-6-FLUOROCINNAMIC ACID
33	Structure1	2-CHLORO-5-(TRIFLUOROMETHYL)BENZOIC ACID

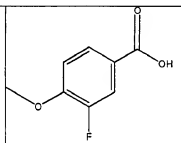
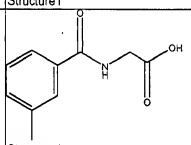
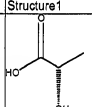
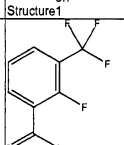
34	 Structure1	3-FLUORO-4-METHOXYBENZOIC ACID
35	 Structure1	3-METHYLHIPPURIC ACID
36	 Structure1	L-LACTIC ACID
37	 Structure1	2-FLUORO-3-(TRIFLUOROMETHYL)BENZOIC ACID

FIG. 4-J

FIG. 4-K

38	Structure1	TRANS-3-(2,5-DIMETHYLBENZOYL)ACRYLIC ACID
39	Structure1	(S)-(-)-TROLOX(R)
40	Structure1	TETRAHYDRO-2-FUROIC ACID
41	Structure1	ALPHA-ETHYL-3-HYDROXY-2,4,6-TRIIODOHYDROCINNAM

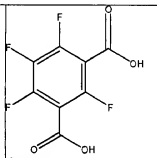
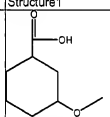
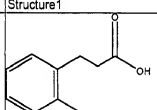
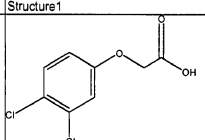
42	 Structure1	TETRAFLUOROISOPHTHALIC ACID
43	 Structure1	3-METHOXYCYCLOHEXANECARBOXYLIC ACID
44	 Structure1	2-METHYLHYDROCINNAMIC ACID
45	 Structure1	3,4-DICHLOROPHENOXYACETIC ACID

FIG. 4-L

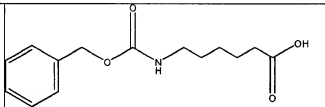
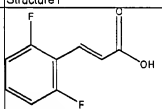
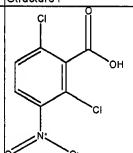
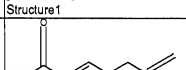
46	 Structure1	6-(CARBOBENZYLOXYAMINO)CAPROIC ACID
47	 Structure1	TRANS-2,6-DIFLUOROCINNAMIC ACID
48	 Structure1	2,6-DICHLORO-3-NITROBENZOIC ACID
49	 Structure1	2,6-HEPTADIENOIC ACID

FIG. 4-M

FIG. 4-N

50	Structure1	(R)-(+)-2-PYRROLIDONE-5-CARBOXYLIC ACID
51	Structure1	(R)-(+)-CITRONELLIC ACID
52	Structure1	1,1-CYCLOPROPANEDICARBOXYLIC ACID
53	Structure1	2-METHYLHEXANOIC ACID
54	Structure1	1-CYANO-1-CYCLOPROPANECARBOXYLIC ACID

FIG. 4-O

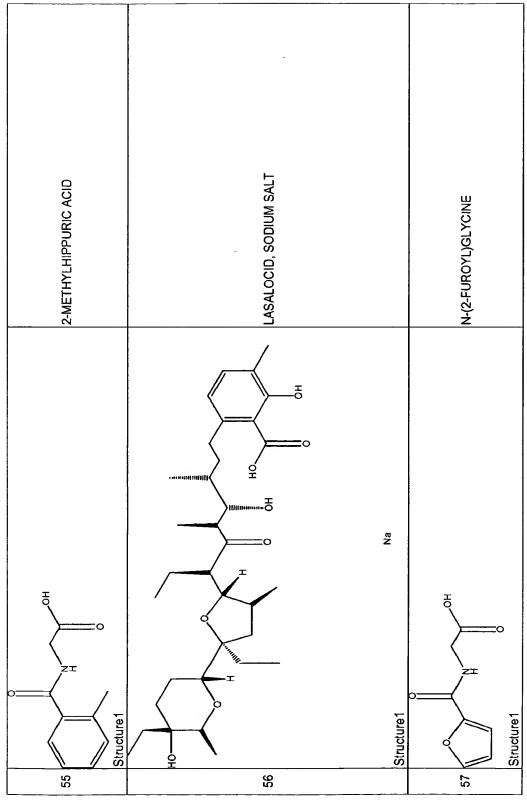

55
Structure1
2-METHYLHIPPURIC ACID
56
Structure1
LASALOCID, SODIUM SALT
Na
57
Structure1
N-(2-FUROYL)GLYCINE

FIG. 4-P

58	Structure1	3,5-DIFLUOROCINNAMIC ACID
59	Structure1	1-ISOQUINOLINECARBOXYLIC ACID
60	Structure1	(S)-(+)-HEXAHYDROMANDELIC ACID
61	Structure1	2,6-DIFLUOROPHENYLACETIC ACID

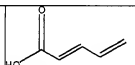
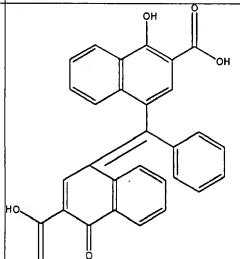
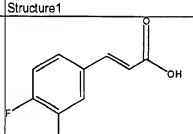
62	 Structure1	TRANS-2,4-PENTADIENOIC ACID
63	 Structure1 Na	NAPHTHOCHROME GREEN
64	 Structure1	TRANS-3,4-DIFLUOROCINNAMIC ACID

FIG. 4-Q

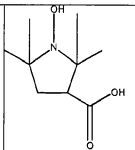
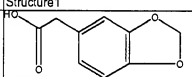
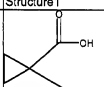
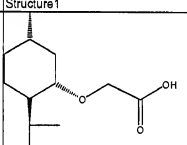
65	 Structure1	3-CARBOXY-PROXYL
66	 Structure1	3,4-(METHYLENEDIOXY)PHENYLACETIC ACID
67	 Structure1	1-METHYLCYCLOPROPANECARBOXYLIC ACID
68	 Structure1	(+)-MENTHOXYACETIC ACID

FIG. 4-R

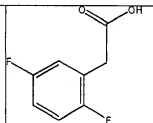
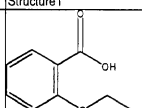
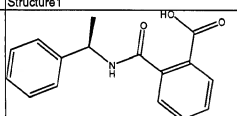
69	 Structure1	2,5-DIFLUOROPHENYLACETIC ACID
70	 Structure1	2-ETHOXYBENZOIC ACID
71	 Structure1	S(-)-N-(alpha-Methylbenzyl)phthalic acid monoamide

FIG. 4-S

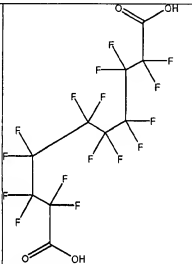
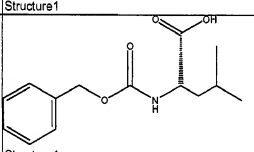
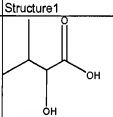
72	 Structure1	PERFLUOROSEBACIC ACID
73	 Structure1	N-CARBOBENZYLOXY-L-LEUCINE
74	 Structure1	2-HYDROXY-3-METHYLBUTYRIC ACID

FIG. 4-T

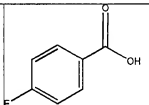
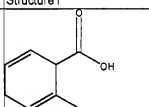
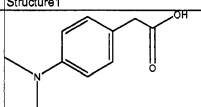
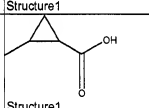
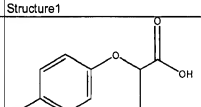
75	 Structure1	4-FLUOROBENZOIC ACID
76	 Structure1	1,4-DIHYDRO-2-METHYLBENZOIC ACID
77	 Structure1	4-(DIMETHYLAMINO)PHENYLACETIC ACID
78	 Structure1	2-METHYLCYCLOPROPANECARBOXYLIC ACID
79	 Structure1	2-(4-HYDROXYPHENOXY)PROPIONIC ACID

FIG. 4-U

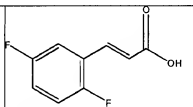
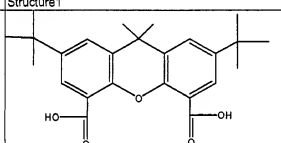
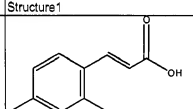
80	 Structure1	TRANS-2,5-DIFLUOROCINNAMIC ACID
81	 Structure1	1-METHYL-1-CYCLOHEXANECARBOXYLIC ACID
82	 Structure1	2,7-DI-TERT-BUTYL-9,9-DIMETHYL-4,5-XANTHENEDICARI
83	 Structure1	TRANS-2,4-DIFLUOROCINNAMIC ACID

FIG. 4-V

FIG. 4-W

84	Structure1	4-NITROHIPPURIC ACID
85	Structure1	(S)-(-)-ALPHA-METHOXY-ALPHA-(TRIFLUOROMETHYL)PI-
86	Structure1	(R)-(+)-ALPHA-METHOXY-ALPHA-(TRIFLUOROMETHYL)PI
87	Structure1	DIETHYLPHOSPHONOACETIC ACID

FIG. 4-X

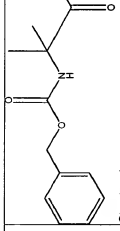
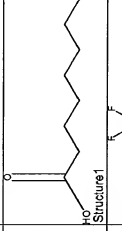
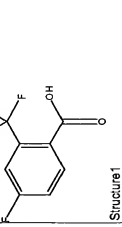
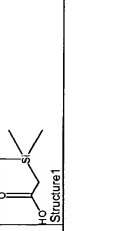
88	 Structure1	N-CARBOBENZYLOXY-2-METHYLALANINE
89	 Structure1	10-UNDECYNOIC ACID
90	 Structure1	4-FLUORO-2-(TRIFLUOROMETHYL)BENZOIC ACID
91	 Structure1	(TRIMETHYLSILYL)ACETIC ACID

FIG. 4-Y

92	Structure1	3-FLUOROPHTHALIC ACID
93	Structure1	TETRAFLUOROPHTHALIC ACID
94	Structure1	3-BROMO-4-FLUOROBENZOIC ACID
95	Structure1	6-PHENYLHEXANOIC ACID

FIG. 4-Z

96	Structure1	2-HYDROXY-6-ISOPROPYL-3-METHYLBENZOIC ACID
97	Structure1	ALPHA-(TERT-BUTYL)HYDROCINNAMIC ACID
98	Structure1	2-HYDROXY-3-ISOPROPYLBENZOIC ACID
99	Structure1	DL-3,4-DIHYDROXYMANDELIC ACID

FIG. 4-AA

100	Structure1	2,3,6-TRIFLUOROBENZOIC ACID
101	Structure1	2-CHLOROPROPIONIC ACID
102	Structure1	CHENODEOXYCHOLIC ACID

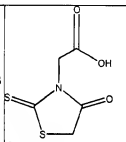
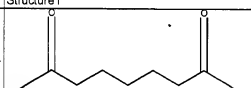
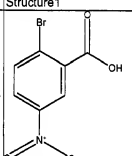
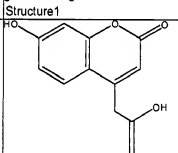
103	 Structure1	RHODANINE-3-ACETIC ACID
104	 Structure1	7-OXOOCTANOIC ACID
105	 Structure1	2-BROMO-5-NITROBENZOIC ACID
106	 Structure1	7-HYDROXYCOUMARIN-4-ACETIC ACID

FIG. 4-AB

FIG. 4-AC

107	Structure1	2-HYDROXY-3-ISOPROPYL-6-METHYLBENZOIC ACID
108	Structure1	2-FLUORO-5-NITROBENZOIC ACID
109	Structure1	N-(3,5-DINITROBENZOYL)-DL-LEUCINE

FIG. 4-AD

110	Structure1	4-HYDROXY-3-NITROPHENYLACETIC ACID
111	Structure1	3-CYANOBENZOIC ACID
112	Structure1	(1R-(2-ENDO,3-EXO))-3-HYDROXY-4,7,7-TRIMETHYLBICY
113	Structure1	(2-NAPHTHOXY)ACETIC ACID

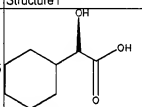
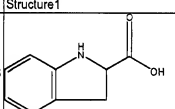
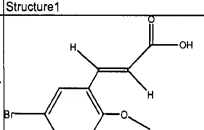
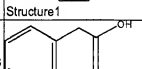
114	 Structure1	2-ETHYLBUTYRIC ACID
115	 Structure1	(R)-(-)-HEXAHYDROMANDELIC ACID
116	 Structure1	(S)-(-)-INDOLINE-2-CARBOXYLIC ACID
117	 Structure1	TRANS-5-BROMO-2-METHOXYCINNAMIC ACID
118	 Structure1	PHENYLACETIC ACID

FIG. 4-AE

FIG. 4-AF

119	Structure1	5-FLUORO-2-METHYLBENZOIC ACID
120	Structure1	(R)-(-)-N-(3,5-DINITROBENZOYL)-ALPHA-PHENYLGLYCINE
121	Structure1	1-PYRENEBUTYRIC ACID
122	Structure1	N-(5-(TRIFLUOROMETHYL)-2-PYRIDYL)-L-VALINE

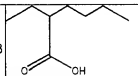
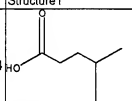
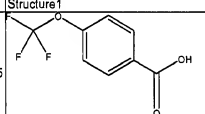
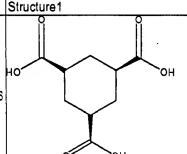
123	 Structure1	2-ETHYLHEXANOIC ACID
124	 Structure1	4-METHYLVALERIC ACID
125	 Structure1	4-(TRIFLUOROMETHOXY)BENZOIC ACID
126	 Structure1	1,3,5-CYCLOHEXANETRICARBOXYLIC ACID

FIG. 4-AG

FIG. 4-AH

127	Structure1	2,4,6-TRICHLOROBENZOIC ACID
128	Structure1	2-METHYL-4-OXO-4-PHENYLBUTYRIC ACID
129	Structure1	1-METHYL-2-CYCLOHEXENE-1-CARBOXYLIC ACID
130	Structure1	(1ALPHA,3ALPHA,5BETA)-1,3,5-TRIMETHYL-1,3,5-CYCLOI

FIG. 4-AI

131	Structure1	2-PHENYLGLUTARIC ANHYDRIDE
132	Structure1	CIS-2-METHOXYCINNAMIC ACID
133	Structure1	(ALPHA,ALPHA,ALPHA-TRIFLUORO-P-TOLYL)ACETIC ACI
134	Structure1	4,5-DIMETHOXY-2-NITROBENZOIC ACID

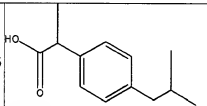
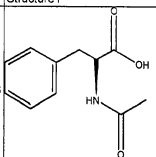
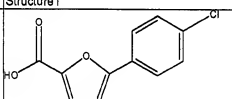
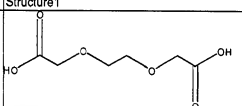
135	 Structure1	4-ISOBUTYL-ALPHA-METHYLPHENYLACETIC ACID
136	 Structure1	N-ACETYL-L-PHENYLALANINE
137	 Structure1	5-(4-CHLOROPHENYL)-2-FUROIC ACID
138	 Structure1	3,6-DIOXAOCTANEDIOIC ACID

FIG. 4-AJ

FIG. 4-AK

139	Structure1	(S)-(-)-2-OXO-1,5-IMIDAZOLIDINEDICARBOXYLIC ACID 1-E
140	Structure1	CIS-ACONITIC ANHYDRIDE
141	Structure1	3-(PHENYLSULFONYL)PROPIONIC ACID
142	Structure1	3-METHYLVALERIC ACID

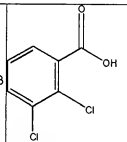
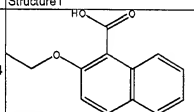
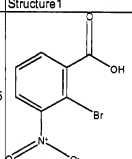
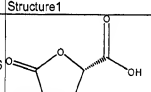
143	 Structure1	2,3-DICHLOROBENZOIC ACID
144	 Structure1	2-ETHOXY-1-NAPHTHOIC ACID
145	 Structure1	2-BROMO-3-NITROBENZOIC ACID
146	 Structure1	(S)-(+)-5-OXO-2-TETRAHYDROFURANCARBOXYLIC ACID

FIG. 4-AL

FIG. 4-AM

147	Structure1	3-CHLORO-2-NITROBENZOIC ACID
148	Structure1	N-P-TOSYLGLYCINE
149	Structure1	3,5-DINITRO-O-TOLUIC ACID
150	Structure1	(1-NAPHTHOXY)ACETIC ACID

FIG. 4-AN

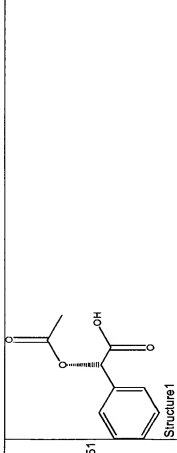
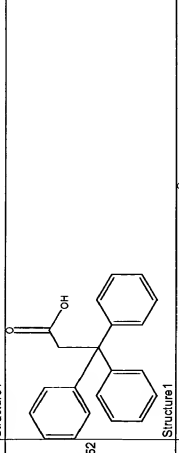
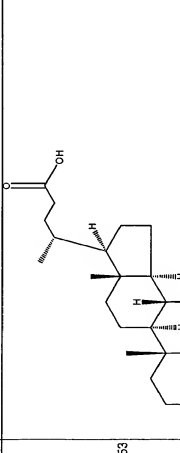
151	 Structure1	(S)-(+)-O-ACETYLMANDELIC ACID
152	 Structure1	3,3,3-TRIPHENYLPROPIONIC ACID
153	 Structure1	URSODEOXYCHOLIC ACID

FIG. 4-AO

154	Structure1	2-THIOPHENEGLYOXYLIC ACID
155	Structure1	ALPHA-METHOXYPHENYLACETIC ACID
156	Structure1	2-HYDROXYCAPROIC ACID
157	Structure1	2,2-BIS(HYDROXYMETHYL)PROPIONIC ACID

FIG. 4-AP

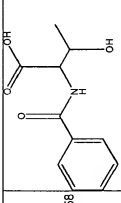
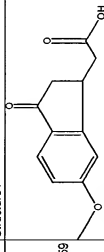
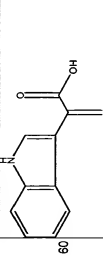
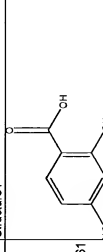
158	 Structure1	N-BENZOYL-L-THREONINE
159	 Structure1	5-METHOXY-1-INDANONE-3-ACETIC ACID
160	 Structure1	3-INDOLEGLYOXYLIC ACID
161	 Structure1	2,3,4-TRIHYDROXYBENZOIC ACID

FIG. 4-AQ

162	Structure1	4-BROMOBENZENESULFONYL CHLORIDE
163	Structure1	INDOLE-4-CARBOXYLIC ACID
164	Structure1	2-FLUOROCINNAMIC ACID
165	Structure1	2,5-BIS(TRIFLUOROMETHYL)BENZOIC ACID

FIG. 4-AR

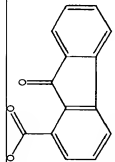
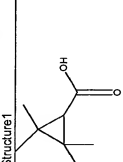
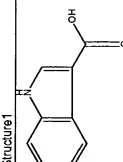
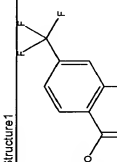
166	 Structure1	9-FLUORENONE-1-CARBOXYLIC ACID
167	 Structure1	2,2,3,3-TETRAMETHYLCYCLOPROPANECARBOXYLIC AC
168	 Structure1	INDOLE-3-CARBOXYLIC ACID
169	 Structure1	2-FLUORO-4-(TRIFLUOROMETHYL)BENZOIC ACID

FIG. 4-AS

170	Structure1	4-(DIMETHYLAMINO)CINNAMIC ACID
171	Structure1	(-)-2-OXO-4-THIAZOLIDINECARBOXYLIC ACID
172	Structure1	3-(TRIFLUOROMETHYL)CINNAMIC ACID
173	Structure1	3-(3-Hydroxyphenyl)propionic acid

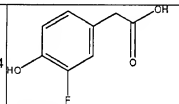
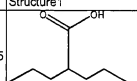
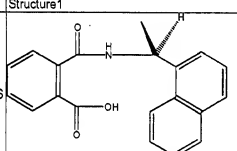
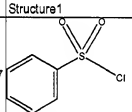
174	 Structure1	3-FLUORO-4-HYDROXYPHENYLACETIC ACID
175	 Structure1	2-PROPYLPENTANOIC ACID
176	 Structure1	N-((S)-1-(1-NAPHTHYL)ETHYL)PHTHALAMIC ACID
177	 Structure1	BENZENESULFONYL CHLORIDE

FIG. 4-AT

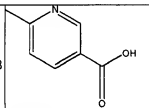
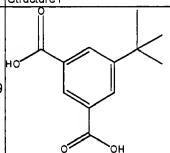
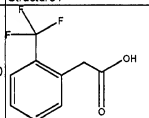
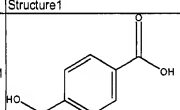
178	 Structure1	6-METHYLNICOTINIC ACID
179	 Structure1	5-TERT-BUTYLISOPHTHALIC ACID
180	 Structure1	(ALPHA,ALPHA,ALPHA-TRIFLUORO-O-TOLYL)ACETIC AC
181	 Structure1	4-(HYDROXYMETHYL)BENZOIC ACID

FIG. 4-AU

FIG. 4-AV

182	Structure1	(S)-(-)-ALPHA-METHOXY-ALPHA-(TRIFLUOROMETHYL)PH
183	Structure1	1,3-ADAMANTANEDIACETIC ACID
184	Structure1	3-HYDROXYBUTYRIC ACID
185	Structure1	2,6-DIMETHYLBENZOIC ACID

FIG. 4-AW

186	Structure1	1-PHENYL-1-CYCLOPROPANECARBOXYLIC ACID
187	Structure1	5-METHOXY-2-METHYL-3-INDOLEACETIC ACID
188	Structure1	3-HYDROXY-2-QUINOXALINECARBOXYLIC ACID
189	Structure1	BIS(4-CHLOROPHENYL)ACETIC ACID

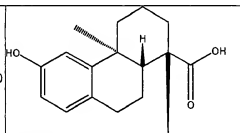
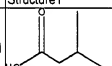
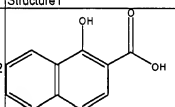
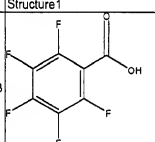
190	 Structure1	PODOCARPIC ACID
191	 Structure1	ISOVALERIC ACID
192	 Structure1	1-HYDROXY-2-NAPHTHOIC ACID
193	 Structure1	PENTAFLUOROBENZOIC ACID

FIG. 4-AX

FIG. 4-AY

194	Structure1	9-FLUORENEACETIC ACID
195	Structure1	4-(TRIFLUOROMETHYL)MANDELIC ACID
196	Structure1	(S)-(-)-2-(PHENYLCARBAMOYLOXY)PROPIONIC ACID
197	Structure1	(R)-(-)-CITRAMALIC ACID

FIG. 4-AZ

198	Structure1	2,3,4,5-TETRAFLUOROBENZOIC ACID
199	Structure1	2,3-DIFLUOROBENZOIC ACID
200	Structure1	2,4-DIFLUOROPHENYLACETIC ACID

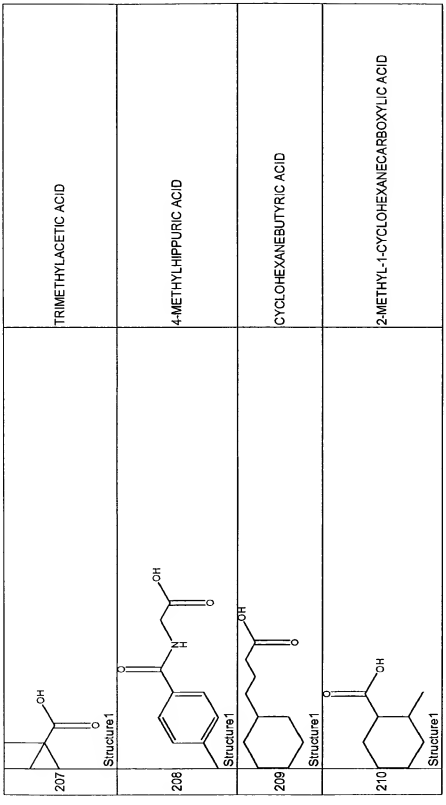
FIG. 4-BA

201	Structure1	VMA
202	Structure1	4-(METHYLTHIO)PHENYLACETIC ACID
203	Structure1	2,2-DIHYDROXY-3,3,3-TRICHLOROPROPIONIC ACID

FIG. 4-BB

204	Structure1	3-SULFOBENZOIC ACID, SODIUM SALT
205	Structure1	4-HYDROXYPHENYLPYRUVIC ACID
206	Structure1	2-NITRO-ALPHA,ALPHA,ALPHA-TRIFLUORO-P-TOLUIC AC

FIG. 4-BC


207
Structure1
TRIMETHYLACETIC ACID
208
Structure1
4-METHYLHIPPURIC ACID
209
Structure1
CYCLOHEXANEBUTYRIC ACID
210
Structure1
2-METHYL-1-CYCLOHEXANECARBOXYLIC ACID

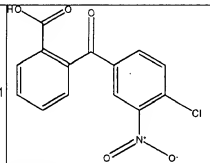
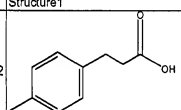
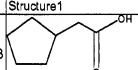
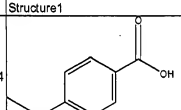
211	 Structure1	2-(4-CHLORO-3-NITROBENZOYL)BENZOIC ACID
212	 Structure1	3-(P-TOLYL)PROPIONIC ACID
213	 Structure1	CYCLOPENTYLACETIC ACID
214	 Structure1	4-(METHYLTHIO)BENZOIC ACID

FIG. 4-BD

FIG. 4-BE

215	Structure1	CHOLIC ACID
216	Structure1	3,5-BIS(TRIFLUOROMETHYL)PHENYLACETIC ACID
217	Structure1	2,3,4,5,6-PENTAFLUOROPHENOXYACETIC ACID

FIG. 4-BF

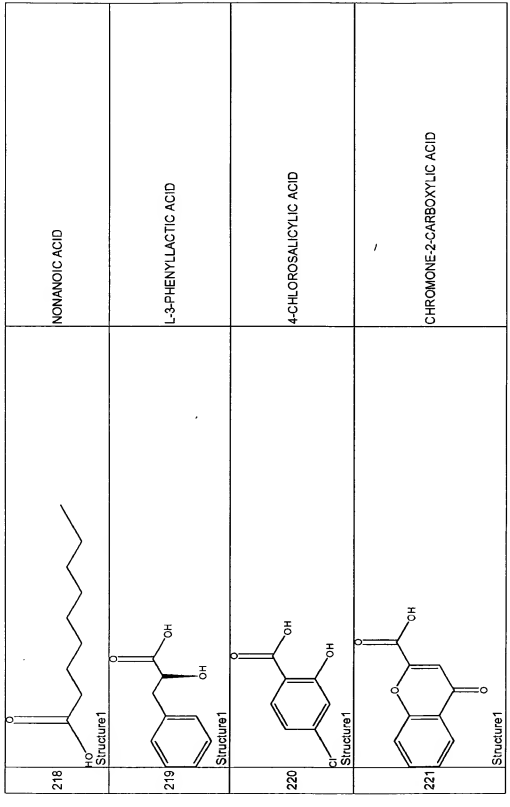

216
Structure1
NONANOIC ACID
219
Structure1
L-3-PHENYLLACTIC ACID
220
Structure1
4-CHLOROSALICYLIC ACID
221
Structure1
CHROMONE-2-CARBOXYLIC ACID

FIG. 4-BG

222	Structure1	YOHIMBINIC ACID MONOHYDRATE
223	Structure1	3-METHYLINDENE-2-CARBOXYLIC ACID
224	Structure1	6-METHYLCHROMONE-2-CARBOXYLIC ACID

FIG. 4-BH

225	Structure1	2-CHLORO-5-(FLUOROSULFONYL)BENZOIC ACID
226	Structure1	4-BUTOXYPHENYLACETIC ACID
227	Structure1	3,4-DIHYDROXYPHENYLACETIC ACID
228	Structure1	(S)-(+)-4-ISOBUTYL-ALPHA-METHYLPHENYLACETIC ACID

FIG. 4-BI

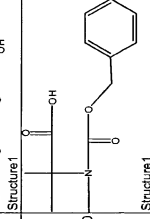
229	 Structure1	3,7-DIHYDROXY-2-NAPHTHOIC ACID
230	Structure1	N-CARBOBENZYLOXY-N,2-DIMETHYLALANINE
231	Structure1	4-PENTENOIC ACID
232	Structure1	6-OXOHEPTANOIC ACID

FIG. 4-BJ

233	Structure1	4-(METHYLSULFONYL)BENZOIC ACID
234	Structure1	4-ETHOXYCARBONYLOXY-3,5-DIMETHOXYBENZOIC ACII
235	Structure1	4-METHYL-1-CYCLOHEXANECARBOXYLIC ACID
236	Structure1	ALPHA,ALPHA,ALPHA-TRIFLUORO-O-TOLUIC ACID

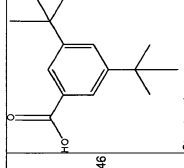
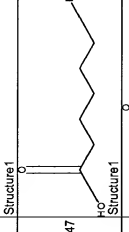
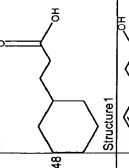
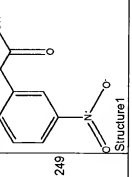
FIG. 4-BK

237	Structure1	3,5,6-TRICHLOROSALICYLIC ACID
238	Structure1	METHOXYACETIC ACID
239	Structure1	6-NITROCAPROIC ACID
240	Structure1	ATROLACTIC ACID HEMIHYDRATE
241	Structure1	MESO-2,3-DIMETHYLSUCCINIC ACID

FIG. 4-BL

242	Structure1	5-CHLORO-O-ANISIC ACID
243	Structure1	2-BROMOACRYLIC ACID
244	Structure1	CYCLOHEXANECARBOXYLIC ACID
245	Structure1	BENZYLMALONIC ACID

FIG. 4-BM

246	 Structure1	3,5-DI-TERT-BUTYLBENZOIC ACID
247	 Structure1	6-BROMOHEXANOIC ACID
248	 Structure1	CYCLOHEXANEPROPIONIC ACID
249	 Structure1	3-NITROPHENYLACETIC ACID

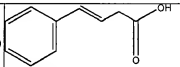
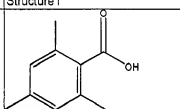
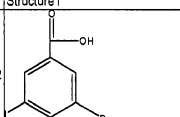
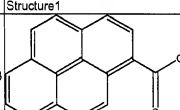
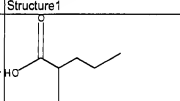
250	 Structure1	TRANS-STYRYLACETIC ACID
251	 Structure1	2,4,6-TRIMETHYLBENZOIC ACID
252	 Structure1	3-BROMO-5-IODOBENZOIC ACID
253	 Structure1	1-PYRENECARBOXYLIC ACID
254	 Structure1	2-METHYLVALERIC ACID

FIG. 4-BN

FIG. 4-BO

255	Structure1	FERROCENECARBOXYLIC ACID
256	Structure1	CYCLOHEXANEPENTANOIC ACID
257	Structure1	R(+)-N-(alpha-Methylbenzyl)phthalic acid monoamide
258	Structure1	(1S)-(+)-CAMPHANIC ACID

FIG. 4-BP

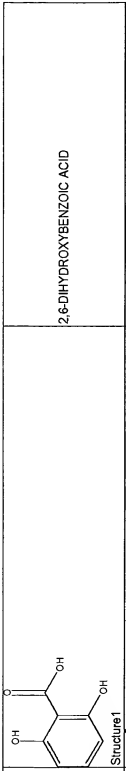
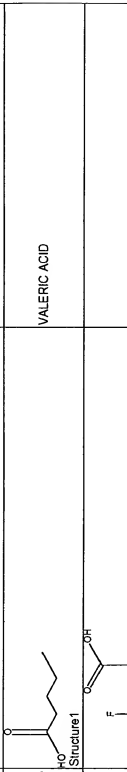
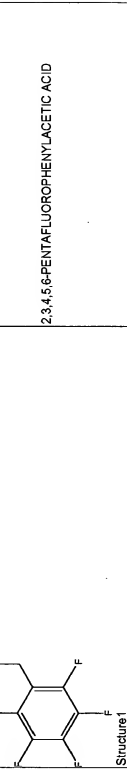
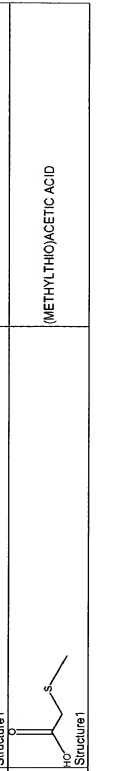
259	 Structure1	2,6-DIHYDROXYBENZOIC ACID
260	 Structure1	VALERIC ACID
261	 Structure1	2,3,4,5,6-PENTAFLUOROPHENYLACETIC ACID
262	 Structure1	(METHYLTHIO)ACETIC ACID

FIG. 4-BQ

263	Structure1	NALPHA-ACETYL-L-ASPARAGINE
264	Structure1	4-HYDROXY-3-METHOXYBENZOIC ACID
265	Structure1	2-NORBORNANEACETIC ACID
266	Structure1	3,4-DIFLUOROBENZOIC ACID

FIG. 4-BR

267	Structure1	2-(2,4,5-TRICHLOROPHENOXY)PROPIONIC ACID
268	Structure1	3-HYDROXY-4-METHOXYCINNAMIC ACID
269	Structure1	TRANS-4-PENTYLCYCLOHEXANECARBOXYLIC ACID

FIG. 4-BS

270	Structure1	ABIETIC ACID
271	Structure1	3,5-DIHYDROXY-2-NAPHTHOIC ACID
272	Structure1	4-CHLOROPHENOXYACETIC ACID

FIG. 4-BT

273	Structure1	(S)-(+)-2-OXO-4-PHENYL-3-OXAZOLIDINEACETIC ACID
274	Structure1	4-FLUORENECARBOXYLIC ACID
275	Structure1	4-OCTYLBENZOIC ACID
276	Structure1	(+)-CARBOBENZYLOXY-D-PROLINE

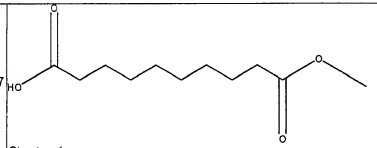
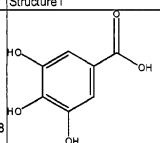
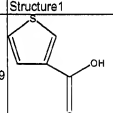
277	 Structure1	SEBACIC ACID MONOMETHYL ESTER
278	 OH_2 Structure1	GALLIC ACID MONOHYDRATE
279	 Structure1	3-THIOPHENECARBOXYLIC ACID

FIG. 4-BU

FIG. 4-BV

280	Structure1	4-HEXYLBENZOIC ACID
281	Structure1	4-FLUORO-1-NAPHTHOIC ACID
282	Structure1	3-NITROPROPIONIC ACID
283	Structure1	5-HYDROXY-2-INDOLECARBOXYLIC ACID

FIG. 4-BW

284	Structure1	3-CHLOROSALICYLIC ACID
285	Structure1	2,3,4-TRIFLUOROCINNAMIC ACID
286	Structure1	(R)-(-)-2-HYDROXY-4-PHENYLBUTYRIC ACID
287	Structure1	PYRUVIC ACID

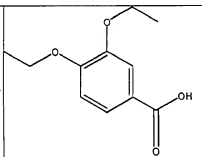
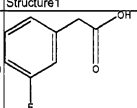
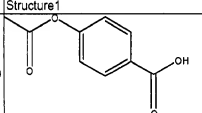
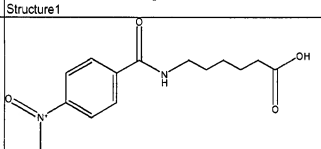
288	 Structure1	3,4-DIETHOXYBENZOIC ACID
289	 Structure1	3-FLUOROPHENYLACETIC ACID
290	 Structure1	4-ACETOXYBENZOIC ACID
291	 Structure1	N-(4-NITROBENZOYL)-6-AMINOCAPROIC ACID

FIG. 4-BX

FIG. 4-BY

292	Structure1	(1S,3R)-(-)-CAMPHORIC ACID
293	Structure1	7-METHOXY-2-BENZOFURANCARBOXYLIC ACID
294	Structure1	2,4,6-TRIFLUOROBENZOIC ACID
295	Structure1	5-OXOAZELAIC ACID

FIG. 4-BZ

296	Structure1	4-(4-METHYLPHENYL)-4-OXOBUTYRIC ACID
297	Structure1	1-NAPHTHOIC ACID
298	Structure1	N-(2,6-DIMETHYLPHENYLCARBAMOYLMETHYL)IMINODIA

FIG. 4-CA

299	Structure1	2-(Benzoyloxymethyl)benzoic acid
300	Structure1	FUSIDIC ACID, SODIUM SALT

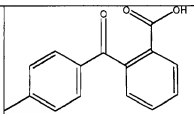
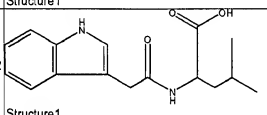
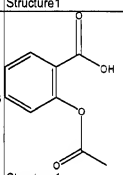
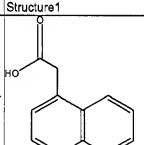
301	 Structure1	2-(P-TOLUOYL)BENZOIC ACID
302	 Structure1	N-(3-INDOLYLACETYL)-L-LEUCINE
303	 Structure1	ACETYLSALICYLIC ACID
304	 Structure1	1-NAPHTHYLACETIC ACID

FIG. 4-CB

FIG. 4-CC

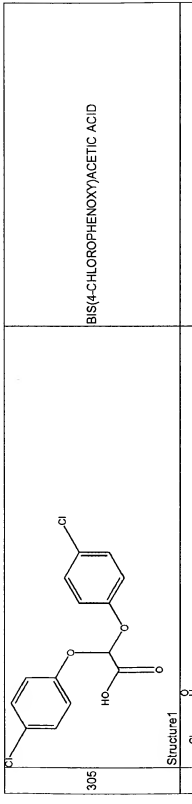
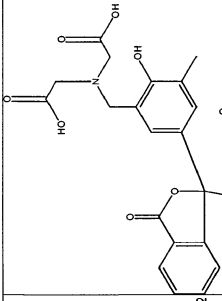

305
Structure1
BIS(4-CHLOROPHENOXY)ACETIC ACID
306
Structure1
2-CHLORO-5-(METHYLTHIO)BENZOIC ACID
307
Structure1
7-(CARBOXYMETHOXY)-4-METHYLCOUMARIN

FIG. 4-CD

308	Structure1	(S)-(+)-ALPHA-HYDROXY-1,3-DIOXO-2-ISOINDOLINEBUTY
309	Structure1	N-CARBOBENZYLOXY-L-GLUTAMIC ACID 1-METHYL EST
310	Structure1	HEPTANOIC ACID
311	Structure1	UNDECYLENIC ACID

FIG. 4-CE

312	 Structure1	O-CRESOLPHTHALEIN COMPLEXONE
313	Structure1	2-(2-CYANOPHENYLTHIO)BENZOIC ACID

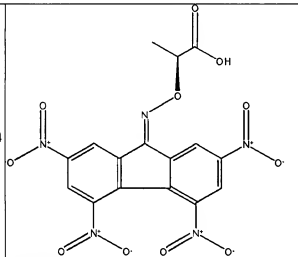
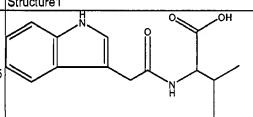
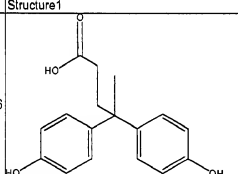
314	 Structure1	(+)-TAPA
315	 Structure1	N-(3-INDOLYLACETYL)-L-VALINE
316	 Structure1	4,4-BIS(4-HYDROXYPHENYL)VALERIC ACID

FIG. 4-CF

FIG. 4-CG

317	Structure1	KEMP'S TRIACID
318	Structure1	3-MALEIMIDOPROPIONIC ACID
319	Structure1	3-NORADAMANTANECARBOXYLIC ACID

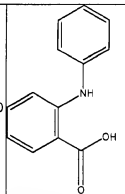
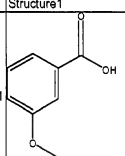
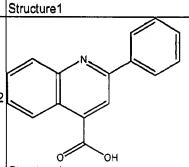
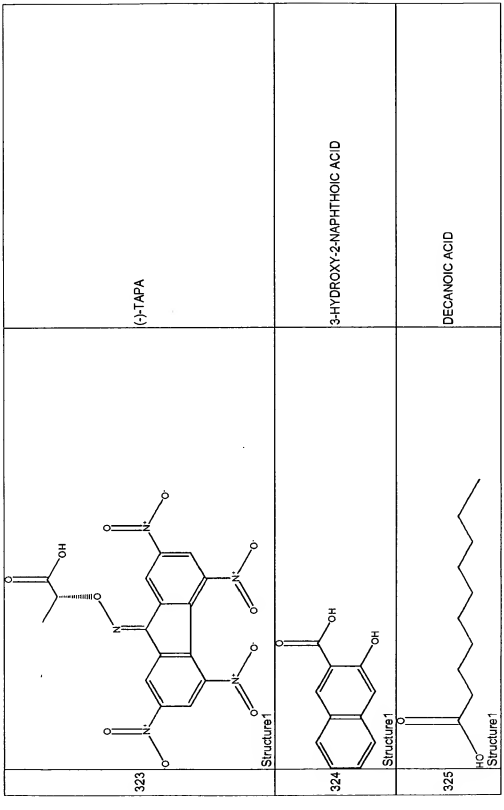
320	 Structure1	N-PHENYLANTHRANILIC ACID
321	 Structure1	M-ANISIC ACID
322	 Structure1	2-PHENYL-4-QUINOLINECARBOXYLIC ACID

FIG. 4-CH

FIG. 4-CI


323
Structure1
(-)-TAPA
324
Structure1
3-HYDROXY-2-NAPHTHOIC ACID
325
Structure1
DECANOIC ACID

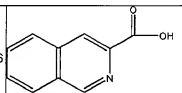
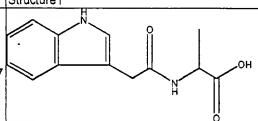
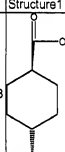
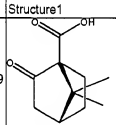
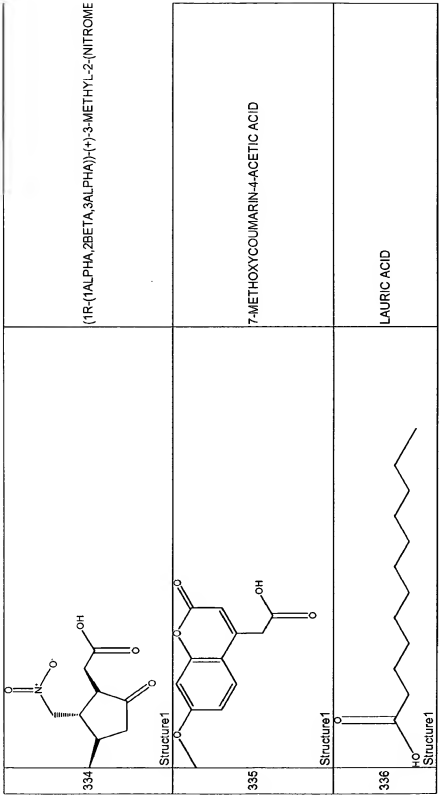
326	 Structure1	3-ISOQUINOLINECARBOXYLIC ACID HYDRATE
327	 Structure1	N-(3-INDOLYLACETYL)-L-ALANINE
328	 Structure1	TRANS-4-METHYL-1-CYCLOHEXANECARBOXYLIC ACID
329	 Structure1	(1S)-(+)-KETOPINIC ACID

FIG. 4-CJ

FIG. 4-CK

330	Structure1	HEPTANOIC ACID
331	Structure1	5-FLUOROSALICYLIC ACID
332	Structure1	2-BROMOBENZOIC ACID
333	Structure1	2-FLUORO-6-(TRIFLUOROMETHYL)BENZOIC ACID

FIG. 4-CL


334
Structure1
(1R-(1ALPHA,2BETA,3ALPHA))-(+)-3-METHYL-2-(NITROME
335
Structure1
7-METHOXYCOUMARIN-4-ACETIC ACID
336
Structure1
LAURIC ACID

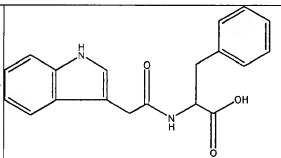
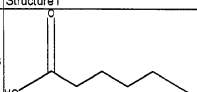
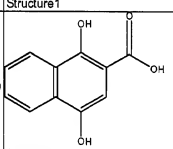
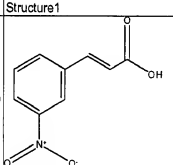
337	 Structure1	N-(3-INDOLYLACETYL)-L-PHENYLALANINE
338	 Structure1	HEXANOIC ACID
339	 Structure1	1,4-DIHYDROXY-2-NAPHTHOIC ACID
340	 Structure1	3-NITROCINNAMIC ACID

FIG. 4-CM

FIG. 4-CN

341	Structure1	2-QUINOXALINECARBOXYLIC ACID
342	Structure1	OCTANOIC ACID
343	Structure1	2,3,5,6-TETRAFLUOROBENZOIC ACID
344	Structure1	4-PYRAZOLECARBOXYLIC ACID

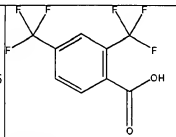
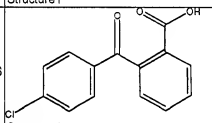
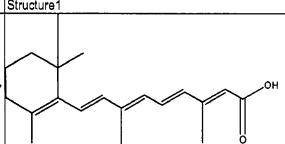
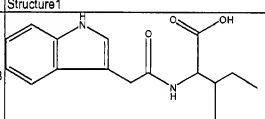
345	 Structure1	2,4-BIS(TRIFLUOROMETHYL)BENZOIC ACID
346	 Structure1	2-(4-CHLOROBENZOYL)BENZOIC ACID
347	 Structure1	ALL-TRANS-RETINOIC ACID
348	 Structure1	N-(3-INDOLYLACETYL)-L-ISOLEUCINE

FIG. 4-CO

FIG. 4-CP

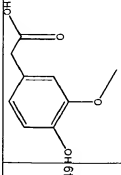
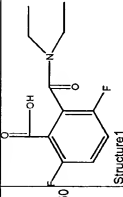
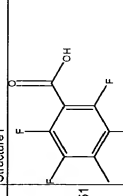
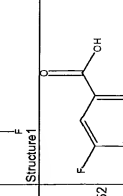
349	 Structure1	HOMOVANILLIC ACID
350	 Structure1	N,N-DIETHYL-3,6-DIFLUOROPHTHALAMIC ACID
351	 Structure1	2,3,5,6-TETRAFLUORO-P-TOLUIC ACID
352	 Structure1	2,4-DICHLORO-5-FLUOROBENZOIC ACID

FIG. 4-CQ

353	Structure1	4-ETHOXYBENZOIC ACID
354	Structure1	2-FLUORO-5-METHYLBENZOIC ACID
355	Structure1	4-PENTYNOIC ACID
356	Structure1	N-((R)-1-(1-NAPHTHYL)ETHYL)PHTHALAMIC ACID

FIG. 4-CR

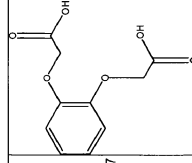
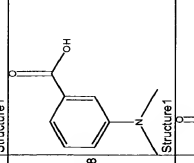
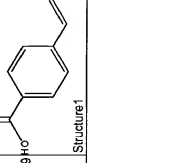
357	 Structure1	1,2-PHENYLENEDIOXYDIACETIC ACID
358	 Structure1	3-DIMETHYLAMINOBENZOIC ACID
359	 Structure1	4-VINYLBENZOIC ACID

FIG. 4-CS

360	Structure1	2,5-DIHYDROXYPHENYLACETIC ACID
361	Structure1	2-THIOPHENEACETIC ACID
362	Structure1	4-ISOPROPOXYBENZOIC ACID
363	Structure1	DIIODOFLUORESCEIN

FIG. 4-CT

364	Structure1	5-NITRO-2-FUROIC ACID
365	Structure1	4-(DIETHYLAMINO)BENZOIC ACID
366	Structure1	3-IODO-4-METHYLBENZOIC ACID
367	Structure1	2-CHLOROPHENYLACETIC ACID

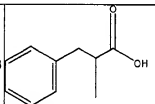
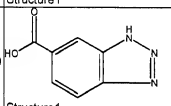
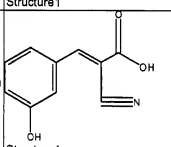
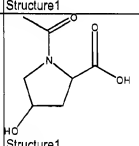
368	 Structure1	ALPHA-METHYLHYDROCINNAMIC ACID
369	 Structure1	BENZOTRIAZOLE-5-CARBOXYLIC ACID
370	 Structure1	ALPHA-CYANO-3-HYDROXYCINNAMIC ACID
371	 Structure1	TRANS-1-ACETYL-4-HYDROXY-L-PROLINE

FIG. 4-CU

FIG. 4-CV

372	Structure1	2-BIBENZYLCARBOXYLIC ACID
373	Structure1	3-(3,4-DIMETHOXYPHENYL)PROPIONIC ACID
374	Structure1	TROLOX(R)

FIG. 4-CW

375	Structure1	TRANS-4-HYDROXY-3-METHOXYCINNAMIC ACID
376	Structure1	AURINTRICARBOXYLIC ACID

FIG. 4-CX

377	Structure1	5-SULFOSALICYLIC ACID DIHYDRATE
378	Structure1	2,3-DIMETHYLBENZOIC ACID
379	Structure1	4-HYDROXY-3-NITROBENZOIC ACID

FIG. 4-CY

380	Structure1	2,4-DIMETHYLBENZOIC ACID
381	Structure1	HIPPURIC ACID
382	Structure1	2,5-DIHYDROXYBENZOIC ACID
383	Structure1	2,3,5-TRIIODOBENZOIC ACID

FIG. 4-CZ

384	Structure1	1-ADAMANTANECARBOXYLIC ACID
385	Structure1	2-ETHYLTHIO-2,2-DIPHENYLACETIC ACID
386	Structure1	5-METHYL-2-NITROBENZOIC ACID
387	Structure1	ETHYLMALONIC ACID

FIG. 4-DA

388	Structure1	3,5-DIBROMO-4-HYDROXYBENZOIC ACID
389	Structure1	2-CHLORO-4-FLUOROBENZOIC ACID
390	Structure1	SULFOACETIC ACID
391	Structure1	3-PHENYLBUTYRIC ACID

FIG. 4-DB

392	Structure1	N-CARBOBENZYLOXY-L-ISOLEUCINE
393	Structure1	(R)-(-)-3-CHLOROMANDELIC ACID
394	Structure1	2-CARBOXYETHYLPHOSPHONIC ACID
395	Structure1	1,3,5-BENZENETRICARBOXYLIC ACID

FIG. 4-DC

396	Structure1	2,4-DIFLUOROBENZOIC ACID
397	Structure1	DIGLYCOLIC ACID
398	Structure1	2,4-DICHLORO-5-SULFAMOYLBENZOIC ACID
399	Structure1	4-BROMO-3,5-DIHYDROXYBENZOIC ACID

FIG. 4-DD

400	Structure1	4-HYDROXY-3,5-DINITROBENZOIC ACID
401	Structure1	2,3,4,5,6-PENTAFLUOROCINNAMIC ACID
402	Structure1	2,4-DICHLOROPHENYLACETIC ACID

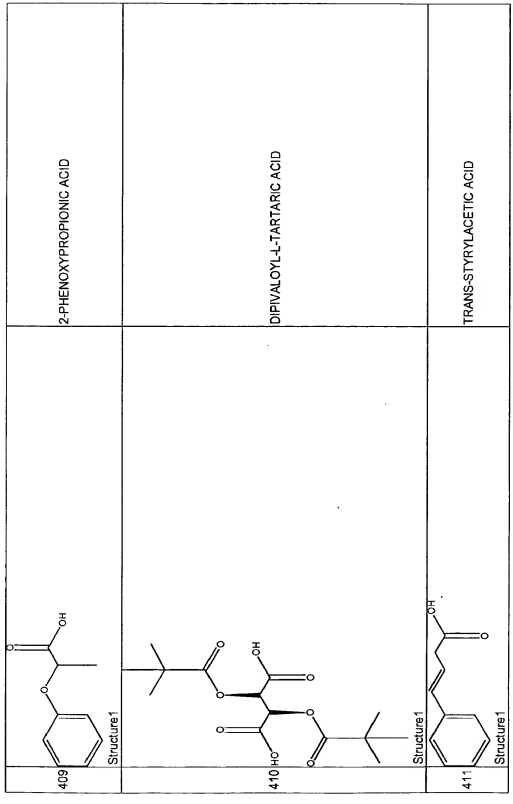
FIG. 4-DE

403		(4-CARBOXYBUTYL)TRIPHENYLPHOSPHONIUM BROMID
404		4-(4-METHOXYPHENYL)BUTYRIC ACID
405		(R)-(+)-TROLOX(R)

FIG. 4-DF

406	HCl Structure1	GALLOCYANINE
407	Structure1	2-METHOXYPHENYLACETIC ACID
408	Structure1	S-(THIOBENZOYL)THIOGLYCOLIC ACID

FIG. 4-DG


409
Structure1
2-PHENOXYPROPIONIC ACID
410
Structure1
DIPIVALOYL-L-TARTARIC ACID
411
Structure1
TRANS-STYRYLACETIC ACID

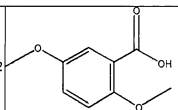
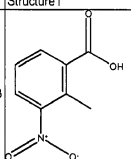
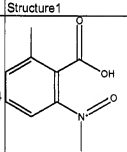
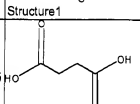
412	 Structure1	2,5-DIMETHOXYBENZOIC ACID
413	 Structure1	2-METHYL-3-NITROBENZOIC ACID
414	 Structure1	2-METHYL-6-NITROBENZOIC ACID
415	 Structure1	SUCCINIC ACID

FIG. 4-DH

FIG. 4-DI

416	Structure1	FUSARIC ACID
417	Structure1	BIS(CARBOXYMETHYL) TRITHIOCARBONATE
418	Structure1	2-CHLORONICOTINIC ACID
419	Structure1	CARBOBENZYLOXY-L-ALANINE

FIG. 4-DJ

420	Structure1	SEBACIC ACID
421	Structure1	PHENYLPHOSPHONIC DICHLORIDE
422	Structure1	P-ANISIC ACID
423	Structure1	2,3,5,6-TETRAFLUORO-4-HYDROXYBENZOIC ACID HYDR

FIG. 4-DK

424	Structure1	2-FLUOROPHENYLACETIC ACID
425	Structure1	1,3-CYCLOHEXANEDICARBOXYLIC ACID
426	Structure1	3-INDOLEBUTYRIC ACID
427	Structure1	2,3-DIHYDROXYBENZOIC ACID

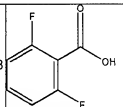
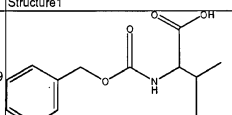
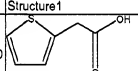
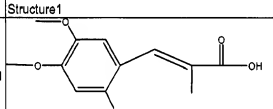
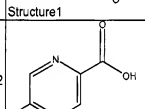
428	 Structure1	2,6-DIFLUOROBENZOIC ACID
429	 Structure1	CARBOBENZYLOXY-L-VALINE
430	 Structure1	2-THIOPHENEACETIC ACID
431	 Structure1	ALPHA-METHYL-2,4,5-TRIMETHOXYCINNAMIC ACID
432	 Structure1	5-METHYL-2-PYRAZINECARBOXYLIC ACID

FIG. 4-DL

FIG. 4-DM

433	Structure1	1,1-CYCLOHEXANEDIACETIC ACID
434	Structure1	3-METHYLSALICYLIC ACID
435	Structure1	2,5-DICHLOROBENZENESULFONYL CHLORIDE
436	Structure1	TRANS-3-(4-METHYLBENZOYL)ACRYLIC ACID

FIG. 4-DN

437	Structure1	2,5-THIOPHENEDICARBOXYLIC ACID
438	Structure1	DI-P-TOLUOYL-L-TARTARIC ACID
439	Structure1	4-METHOXYSALICYLIC ACID
440	Structure1	3,5-DINITRO-P-TOLUIC ACID

FIG. 4-DO

441	Structure1	4-ETHYLBENZOIC ACID
442	Structure1	5,6-DICHLORONICOTINIC ACID
443	Structure1	2-BROMOPHENYLACETIC ACID
444	Structure1	3,5-DI-TERT-BUTYL-4-HYDROXYBENZOIC ACID

FIG. 4-DP

445	Structure1	5-METHOXYSALICYLIC ACID
446	Structure1	4-(2,4-DICHLOROPHENOXY)BUTYRIC ACID
447	Structure1	4-FLUOROBENZOIC ACID
448	Structure1	2-CHLORO-3-NITROBENZOIC ACID

FIG. 4-DQ

449	Structure1	1-METHYLINDOLE-2-CARBOXYLIC ACID
450	Structure1	4-ACETYLBENZOIC ACID
451	Structure1	2-[2-[2-METHOXYETHOXY]ETHOXY]ACETIC ACID
452	Structure1	3,4-DIHYDROXYBENZOIC ACID

FIG. 4-DR

453	Structure1	4-HYDROXYPHENYLACETIC ACID
454	Structure1	BENZOYLFORMIC ACID
455	Structure1	2,4-DIHYDROXYBENZOIC ACID
456	Structure1	4-TERT-BUTYLBENZENESULFONYL CHLORIDE

FIG. 4-DS

457	Structure1	6-ACETAMIDOHEXANOIC ACID
458	Structure1	2-THIOPHENEACETIC ACID
459	Structure1	3-NITROBENZENESULFONYL CHLORIDE
460	Structure1	TRANS-2-HEXENOIC ACID

FIG. 4-DT

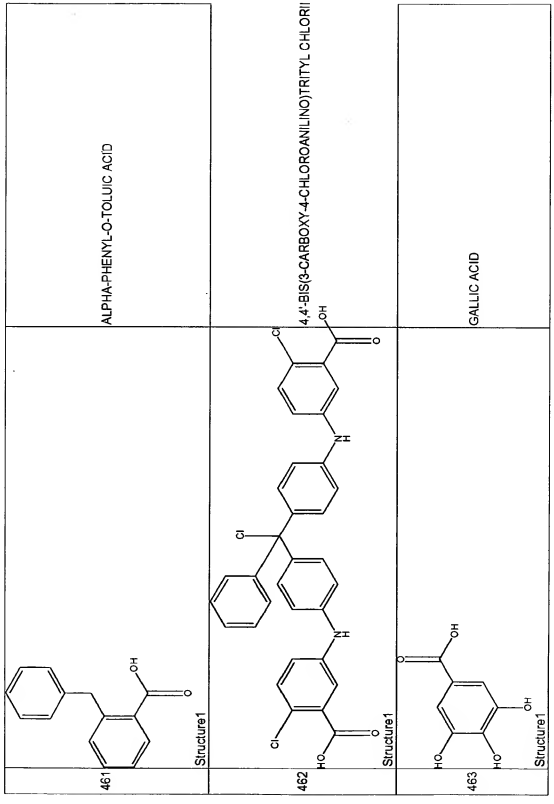

461
Structure1
ALPHA-PHENYL-O-TOLUIC ACID
462
Structure1
4,4'-BIS(3-CARBOXY-4-CHLOROANILINO)TRITYL CHLORII
463
Structure1
GALLIC ACID

FIG. 4-DU

464	Structure1	3-HYDROXYBENZOIC ACID
465	Structure1	2-NAPHTHOIC ACID
466	Structure1	3,5-DINITROBENZOIC ACID

FIG. 4-DV

467	Structure1	4,4'-(HEXAFLUOROISOPROPYLIDENE)BIS(BENZOIC ACID
468	Structure1	4-BROMOCINNAMIC ACID
469	Structure1	3-HYDROXY-4-METHOXYBENZOIC ACID
470	Structure1	2-CHLOROBENZOIC ACID

FIG. 4-DW

471	Structure1	3,5-DICHLOROSALICYLIC ACID
472	Structure1	4-BROMOISOPHTHALIC ACID
473	Structure1	GLYCOLIC ACID
474	Structure1	3-(3,4,5-TRIMETHOXYPHENYL)PROPIONIC ACID

FIG. 4-DX

475		3-(4-HYDROXYPHENYL)PROPIONIC ACID
476		4-BIPHENYLACETIC ACID
477		(1R,3R,4R,5R)-(-)-QUINIC ACID
478		4-(4-NITROPHENYL)BUTYRIC ACID

FIG. 4-DY

479	Structure1	2-HYDROXYPHENYLACETIC ACID
480	Structure1	3-BROMOCINNAMIC ACID
481	Structure1	ADIPIC ACID MONOETHYL ESTER
482	Structure1	2-(2,4-DICHLOROPHENOXY)PROPIONIC ACID

FIG. 4-DZ

483	Structure1	SUCCINAMIC ACID
484	Structure1	DIETHYLMALONIC ACID
485	Structure1	3-PHENOXYBENZOIC ACID
486	Structure1	TRIPHENYLACETIC ACID

FIG. 4-EA

487	Structure1	BENZILIC ACID
488	Structure1	3-HYDROXYPHENYLACETIC ACID
489	Structure1	(R)-(-)-MANDELIC ACID
490	Structure1	HYDROCINNAMIC ACID

FIG. 4-EB

491	Structure1	4-CHLORO-O-TOLYLOXYACETIC ACID
492	Structure1	2,4,5-TRICHLOROPHENOXYACETIC ACID
493	Structure1	3,4-DICHLOROPHENYLACETIC ACID
494	Structure1	ALPHA-TOLUENESULFONYL CHLORIDE

FIG. 4-EC

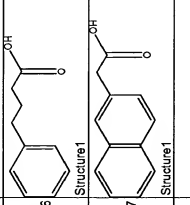
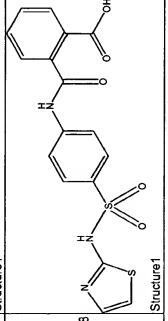
495	 Structure1	MONO-METHYL TEREPHTHALATE
496	 Structure1	4-PHENYLBUTYRIC ACID
497	Structure1	2-NAPHTHYLACETIC ACID
498	 Structure1	PHTHALYLSULFATHIAZOLE

FIG. 4-ED

499	Structure1	DIPHENYLACETIC ACID
500	Structure1	2-BIPHENYLCARBOXYLIC ACID
501	Structure1	4-(4-(2-CARBOXYBENZOYL)PHENYL)BUTYRIC ACID
502	Structure1	ALPHA-PHENYLCYCLOPENTANEACETIC ACID

FIG. 4-EE

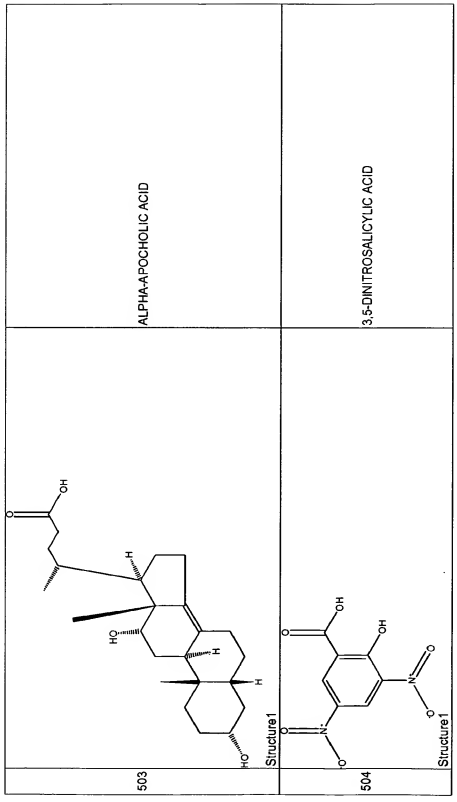

503
Structure1
ALPHA-APOCHOLIC ACID
504
Structure1
3,5-DINITROSALICYLIC ACID

FIG. 4-EF

505	Structure1	3-BROMOBENZOIC ACID
506	Structure1	3-METHOXY-4-NITROBENZOIC ACID
507	Structure1	ANTHRANILIC ACID
508	Structure1	PROPIONIC ACID

FIG. 4-EG

509	Structure1	4-OXO-6-PHENYL-5-HEXENOIC ACID
510	Structure1	1,2,4,5-BENZENETETRACARBOXYLIC DIANHYDRIDE
511	Structure1	4-(2-PHENOXYETHOXY)BENZOIC ACID

FIG. 4-EH

512	Structure1	5-PHENYLVALERIC ACID
513	Structure1	3-NITROBENZOIC ACID
514	Structure1	4'-ETHYL-4-BIPHENYLCARBOXYLIC ACID
515	Structure1	4-PROPOXYBENZOIC ACID

FIG. 4-EI

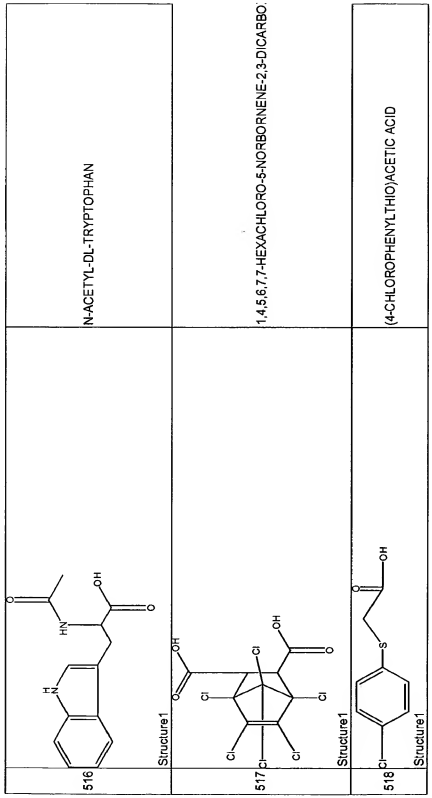

516
Structure1
N-ACETYL-DL-TRYPTOPHAN
517
Structure1
1,4,5,6,7,7-HEXACHLORO-5-NORBORNENE-2,3-DICARBO
518
Structure1
(4-CHLOROPHENYLTHIO)ACETIC ACID

FIG. 4-EJ

519	Structure1	2-PHENOXYBENZOIC ACID
520	Structure1	4-BUTYLBENZOIC ACID
521	Structure1	PHENOXYACETIC ACID
522	Structure1	4-ETHOXYPHENYLACETIC ACID

FIG. 4-EK

523	Structure1	2-NITROPHENYLACETIC ACID
524	Structure1	TRANS-3-(2,3,5,6-TETRAMETHYLBENZOYL)ACRYLIC ACI
525	Structure1	4'-HYDROXY-4-BIPHENYLCARBOXYLIC ACID

FIG. 4-EL

526	Structure1	N-ACETYL-L-METHIONINE
527	Structure1	2-BROMO-5-METHOXYBENZOIC ACID
528	Structure1	PERFLUORO-1-BUTANESULFONYL FLUORIDE

FIG. 4-EM

529	Structure1	2-(2-CHLOROPHENOXY)PROPIONIC ACID
530	Structure1	9-ANTHRACENECARBOXYLIC ACID
531	Structure1	3-HYDROXY-4-NITROBENZOIC ACID
532	Structure1	GLUTARIC ANHYDRIDE

FIG. 4-EN

533	Structure1	3-CHLORO-4-HYDROXYPHENYLACETIC ACID
534	Structure1	2-CHLOROPHENYL DICHLOROPHOSPHATE
535	Structure1	3-(4-CHLOROBENZOYL)PROPIONIC ACID
536	Structure1	4-HYDROXYPHENYLACETIC ACID

FIG. 4-EO

537	Structure1	2-NAPHTHALENESULFONYL CHLORIDE
538	Structure1	DIETHYLMALONIC ACID
539	Structure1	2-FLUOROBENZOIC ACID
540	Structure1	TRANS-2,3-DIMETHOXYCINNAMIC ACID

FIG. 4-EP

541	Structure1	HEPTADECAFLUORONONANOIC ACID
542	Structure1	4-CHLOROBENZENESULFONYL CHLORIDE
543	Structure1	2-CHLORO-4,5-DIFLUOROBENZOIC ACID
544	Structure1	2-THIOPHENEACETIC ACID

FIG. 4-EQ

545	Structure1	DICYCLOHEXYLACETIC ACID
546	Structure1	4-(TRIFLUOROMETHOXY)BENZENESULFONYL CHLORID
547	Structure1	BUTYLMALONIC ACID

FIG. 4-ER

548	Structure1	2-CARBOXYCINNAMIC ACID
549	Structure1	N-(3,5-DINITROBENZOYL)-DL-ALPHA-PHENYLGLYCINE
550	Structure1	ALPHA-CYANO-4-HYDROXYCINNAMIC ACID
551	Structure1	TRANS-3-(4-METHOXYBENZOYL)ACRYLIC ACID

FIG. 4-ES

552	Structure1	S-BENZYL-N-CARBOBENZYLOXY-L-CYSTEINE
553	Structure1	2,2'-IMINODIBENZOIC ACID
554	Structure1	2-HYDROXYHIPPURIC ACID

FIG. 4-ET

555	Structure1	2,4,6-TRIISOPROPYLBENZENESULFONYL CHLORIDE
556	Structure1	TRANS-4-CHLORO-3-NITROCINNAMIC ACID
557	Structure1	1-PHENYL-1-CYCLOPENTANECARBOXYLIC ACID

FIG. 4-EU

558	Structure1	DIBENZOYL-D-TARTARIC ACID
559	Structure1	HABA
560	Structure1	TERT-BUTYLPHOSPHONIC DICHLORIDE
561	Structure1	3-FUROIC ACID

FIG. 4-EV

562	Structure1	(1R)-(-)-10-CAMPHORSULFONYL CHLORIDE
563	Structure1	1-OCTANESULFONYL CHLORIDE
564	Structure1	3-(4-CHLOROBENZOYL)PROPIONIC ACID
565	Structure1	TRANS-3-FLUOROCINNAMIC ACID

FIG. 4-EW

566	Structure1	4-PROPYLBENZOIC ACID
567	Structure1	N-ACETYL-4-FLUORO-DL-PHENYLALANINE
568	Structure1	1,4-PHENYLENEDIPROPIONIC ACID

FIG. 4-EX

569	Structure1	ALPHA,ALPHA,ALPHA-TRIFLUORO-M-TOLUIC ACID
570	Structure1	4-IODOBENZOIC ACID
571	Structure1	5-HYDROXYISOPHTHALIC ACID

FIG. 4-EY

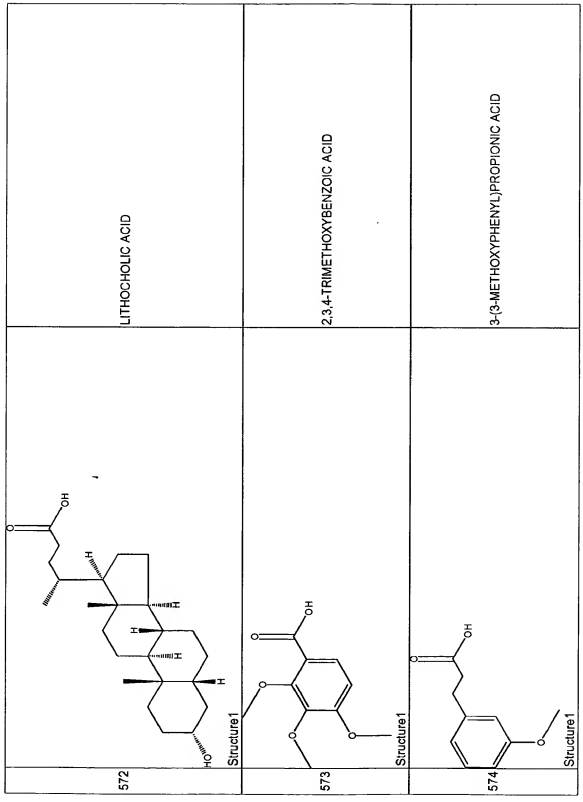

572
LITHOCHOLIC ACID
Structure1
573
2,3,4-TRIMETHOXYBENZOIC ACID
Structure1
574
3-(3-METHOXYPHENYL)PROPIONIC ACID
Structure1

FIG. 4-EZ

575	Structure1	2-HYDROXYISOBUTYRIC ACID
576	Structure1	1,4-CYCLOHEXANEDICARBOXYLIC ACID
577	Structure1	3-BENZOYLBENZOIC ACID
578	Structure1	ALPHA-HYDROXYHIPPURIC ACID

FIG. 4-FA

579	Structure1	(+)-6-METHOXY-ALPHA-METHYL-2-NAPHTHALENEACETI
580	Structure1	MONO-METHYL CIS-5-NORBORNENE-ENDO-2,3-DICARB
581	Structure1	N-ACETYL-L-LEUCINE
582	Structure1	4-BROMOPHENYLACETIC ACID

FIG. 4-FB

583	Structure1	3,4-DIHYDROXYHYDROCINNAMIC ACID
584	Structure1	4-BROMOBENZOIC ACID
585	Structure1	2-NITROBENZOIC ACID
586	Structure1	AZELAIC ACID

FIG. 4-FC

587	Structure1	2-METHYLCINNAMIC ACID
588	Structure1	TRANS-3-FURANACRYLIC ACID
589	Structure1	(1S)-(+)-10-CAMPHORSULFONYL CHLORIDE
590	Structure1	4-FLUORO-3-NITROBENZOIC ACID

FIG. 4-FD

591	Structure1	DI-P-TOLUOYL-D-TARTARIC ACID
592	Structure1	2-CHLORO-5-NITROCINNAMIC ACID
593	Structure1	2-CHLORO-5-NITROBENZOIC ACID

FIG. 4-FE

594	Structure1	TRANS-3-(4-ETHOXYBENZOYL)ACRYLIC ACID
595	Structure1	2-CHLORO-6-FLUOROPHENYLACETIC ACID
596	Structure1	2-THIOPHENEACETIC ACID
597	Structure1	2-HYDROXYISOBUTYRIC ACID

FIG. 4-FF

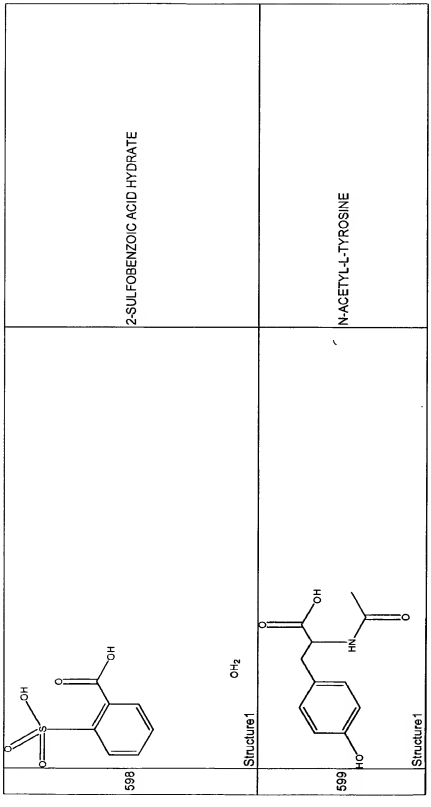

598
Structure1
2-SULFOBENZOIC ACID HYDRATE
599
Structure1
N-ACETYL-L-TYROSINE

FIG. 4-FG

600		N-ETHOXYCARBONYL-L-PHENYLALANINE
601		5-FLUOROINDOLE-2-CARBOXYLIC ACID
602		4-PENTYLBENZOIC ACID
603		3-FLUORO-2-METHYLBENZOIC ACID

FIG. 4-FH

604
TRANS-1,2-CYCLOHEXANEDICARBOXYLIC ACID
Structure1
605
(ALPHA,ALPHA,ALPHA-TRIFLUORO-M-TOLYL)ACETIC AC
Structure1
606
4-CHLOROPHENYLACETIC ACID
Structure1
607
P-TOLUENESULFONYL CHLORIDE
Structure1

FIG. 4-FI

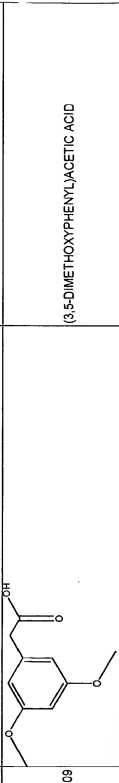
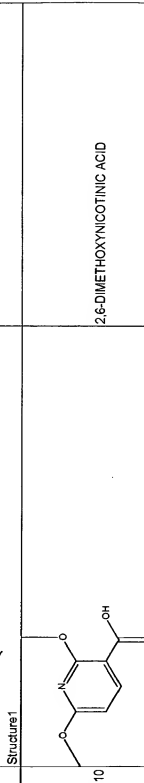
608	 Structure1	N-(CARBOBENZYLOXY)-L-PHENYLALANINE
609	 Structure1	(3,5-DIMETHOXYPHENYL)ACETIC ACID
610	 Structure1	2,6-DIMETHOXYNICOTINIC ACID

FIG. 4-FJ

611	Structure1	5-METHOXY-2-NITROBENZOIC ACID
612	Structure1	5-HYDANTOINACETIC ACID
613	Structure1	CARBOBENZYLOXY-L-GLUTAMINE
614	Structure1	3-BROMO-4-METHYLBENZOIC ACID

FIG. 4-FK

615	Structure1	(2-PYRIMIDYLTHIO)ACETIC ACID
616	Structure1	4-METHOXYCYCLOHEXANECARBOXYLIC ACID
617	Structure1	2,4-DICHLOROBENZOIC ACID
618	Structure1	4,4'-AZOBIS(4-CYANOVALERIC ACID)

FIG. 4-FL

619	Structure1	N-CARBOBENZYLOXY-L-THREONINE
620	Structure1	3,4-(METHYLENEDIOXY)CINNAMIC ACID
621	Structure1	DIPHENIC ACID
622	Structure1	L-MALIC ACID

FIG. 4-FM

623	Structure1	ACETYLSALICYLIC ACID
624	Structure1	2,5-DICHLOROBENZOIC ACID
625	Structure1	2,4-DINITROBENZENESULFONYL CHLORIDE
626	Structure1	6-CHLORONICOTINIC ACID

FIG. 4-FN

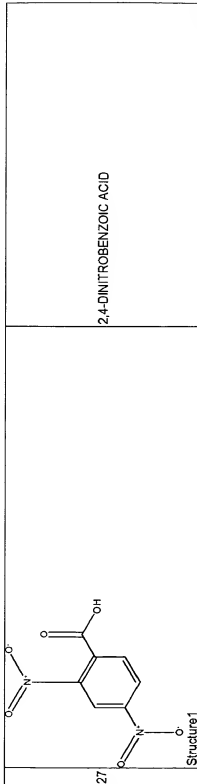
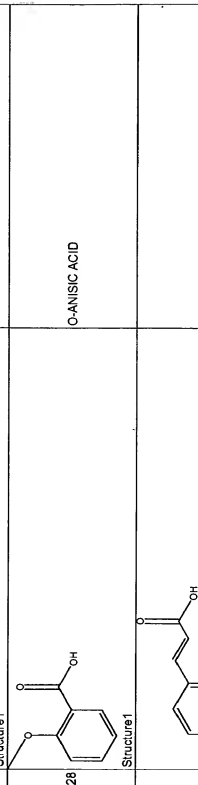
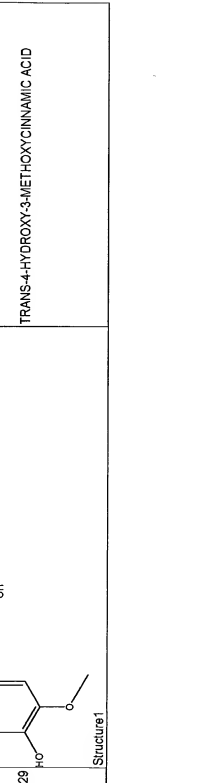
627	 Structure1	2,4-DINITROBENZOIC ACID
628	 Structure1	O-ANISIC ACID
629	 Structure1	TRANS-4-HYDROXY-3-METHOXYCINNAMIC ACID

FIG. 4-FO

630	Structure1	4-HEXYLOXYBENZOIC ACID
631	Structure1	4-HEPTYLOXYBENZOIC ACID
632	Structure1	2-METHYLBUTYRIC ACID
633	Structure1	2-METHOXY-4-(METHYLTHIO)BENZOIC ACID

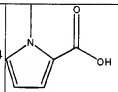
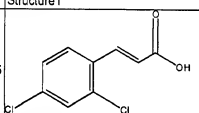
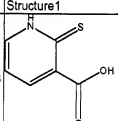
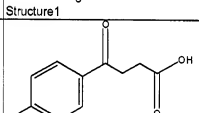
634	 Structure1	1-METHYL-2-PYRROLECARBOXYLIC ACID
635	 Structure1	TRANS-2,4-DICHLOROCINNAMIC ACID
636	 Structure1	2-MERCAPTONICOTINIC ACID
637	 Structure1	3-(4-FLUOROBENZOYL)PROPIONIC ACID

FIG. 4-FP

FIG. 4-FQ

638	Structure1	2-OXO-6-PENTYL-2H-PYRAN-3-CARBOXYLIC ACID
639	Structure1	1-BUTANESULFONYL CHLORIDE
640	Structure1	4-(2,4-DI-TERT-PENTYLPHENOXY)BUTYRIC ACID
641	Structure1	4,4'-OXYBIS(BENZOIC ACID)

FIG. 4-FR

642	Structure1	3-IODOBENZOIC ACID
643	Structure1	1-(4-CHLOROPHENYL)-1-CYCLOPENTANECARBOXYLIC A

FIG. 4-FS

644		CHROME AZUROL S
645		HEXYLPHOSPHONIC DICHLORIDE
646		4-NONYLOXYBENZOIC ACID

FIG. 4-FT

647	Structure1	2-ETHYL-2-HYDROXYBUTYRIC ACID
648	Structure1	1-NAPHTHALENESULFONYL CHLORIDE
649	Structure1	3-(TRIFLUOROMETHYL)BENZENESULFONYL CHLORIDE
650	Structure1	GERANIC ACID

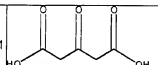
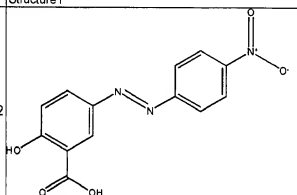
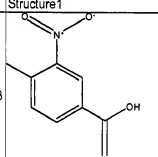
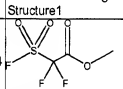
651	 Structure1	1,3-ACETONEDICARBOXYLIC ACID
652	 Structure1	MORDANT ORANGE 1
653	 Structure1	4-METHYL-3-NITROBENZOIC ACID
654	 Structure1	METHYL 2,2-DIFLUORO-2-(FLUOROSULFONYL)ACETATE

FIG. 4-FU

FIG. 4-FV

655	Structure1	3-(2-THIENYL)ACRYLIC ACID
656	Structure1	2-NITRO-4-(TRIFLUOROMETHYL)BENZENESULFONYL CH
657	Structure1	CROTONIC ACID
658	Structure1	N-P-TOSYL-L-PHENYLALANINE

FIG. 4-FW

659	Structure1	4-CHLOROPHENYL DICHLOROPHOSPHATE
660	Structure1	4-(3,4-DIMETHOXYPHENYL)BUTYRIC ACID
661	Structure1	3,3,3-TRIS(4-CHLOROPHENYL)PROPIONIC ACID
662	Structure1	PIPSYL CHLORIDE

FIG. 4-FX

663	Structure1	(2,4-DI-TERT-PENTYLPHENOXY)ACETIC ACID
664	Structure1	MALEAMIC ACID
665	Structure1	4-BUTOXYBENZOIC ACID
666	Structure1	4-METHOXY-3-NITROBENZOIC ACID

FIG. 4-FY

667	Structure1	2,4,6-TRIHYDROXYBENZOIC ACID MONOHYDRATE
668	Structure1	FLUFENAMIC ACID
669	Structure1	ALPHA-ACETAMIDOCINNAMIC ACID

FIG. 4-FZ

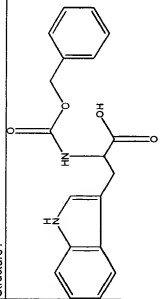
670	 Structure1	2,4-HEXADIENOIC ACID
671	 Structure1	NALPHA-CARBOBENZYLOXY-L-TRYPTOPHAN
672	Structure1	FUMARIC ACID MONOETHYL ESTER
673	Structure1	4-CHLOROBENZOIC ACID

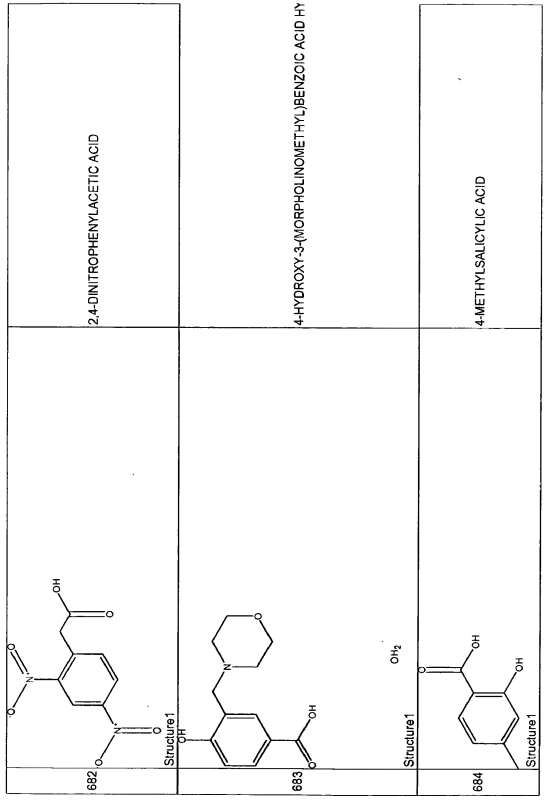
FIG. 4-GA

674	Structure1	3,4-DICHLOROBENZOIC ACID
675	Structure1	TETRAFLUOROPHTHALIC ANHYDRIDE
676	Structure1	PHENYLMALONIC ACID
677	Structure1	4-TERT-BUTYLBENZOIC ACID

FIG. 4-GB

678	Structure1	3-(2-HYDROXYPHENYL)PROPIONIC ACID
679	Structure1	SUCCINIC 2,2-DIMETHYLHYDRAZIDE
680	Structure1	2-(3-CHLOROPHENOXY)PROPIONIC ACID
681	Structure1	2-CHLORO-6-FLUOROBENZOIC ACID

FIG. 4-GC


682
2,4-DINITROPHENYLACETIC ACID
Structure1
683
4-HYDROXY-3-(MORPHOLINOMETHYL)BENZOIC ACID HY
Structure1
684
4-METHYLSALICYLIC ACID
Structure1

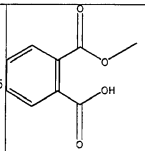
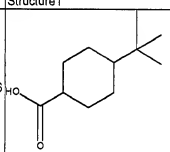
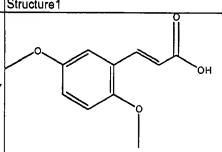
685	 Structure1	MONO-METHYL PHTHALATE
686	 Structure1	4-TERT-BUTYLCYCLOHEXANECARBOXYLIC ACID
687	 Structure1	2,5-DIMETHOXYCINNAMIC ACID

FIG. 4-GD

FIG. 4-GE

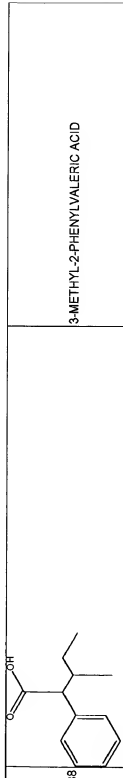
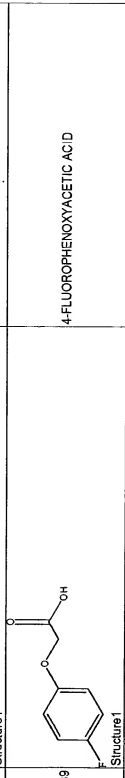
688	 Structure1	3-METHYL-2-PHENYLVALERIC ACID
689	 Structure1	4-FLUOROPHENOXYACETIC ACID
690	 Structure1	2-HYDROXYNICOTINIC ACID

FIG. 4-GF

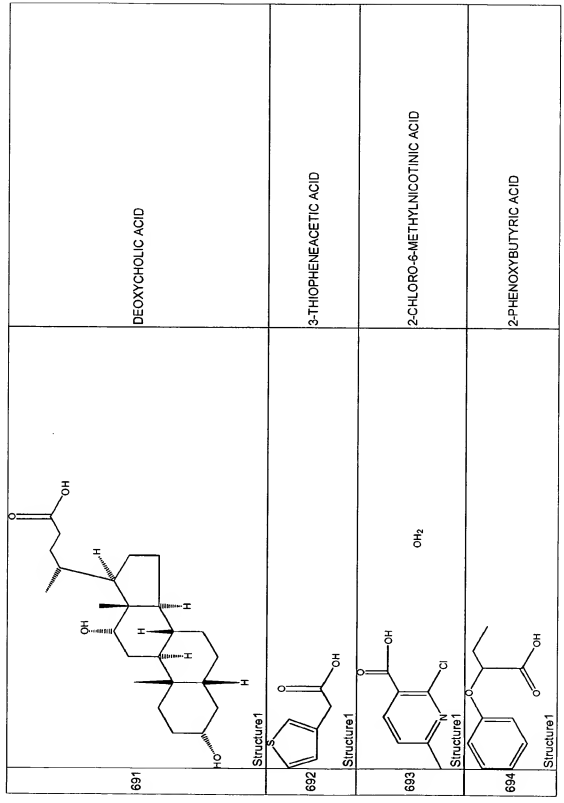

691
DEOXYCHOLIC ACID
Structure1
692
3-THIOPHENEACETIC ACID
Structure1
693
2-CHLORO-6-METHYLNICOTINIC ACID
Structure1
694
2-PHENOXYBUTYRIC ACID
Structure1

FIG. 4-GG

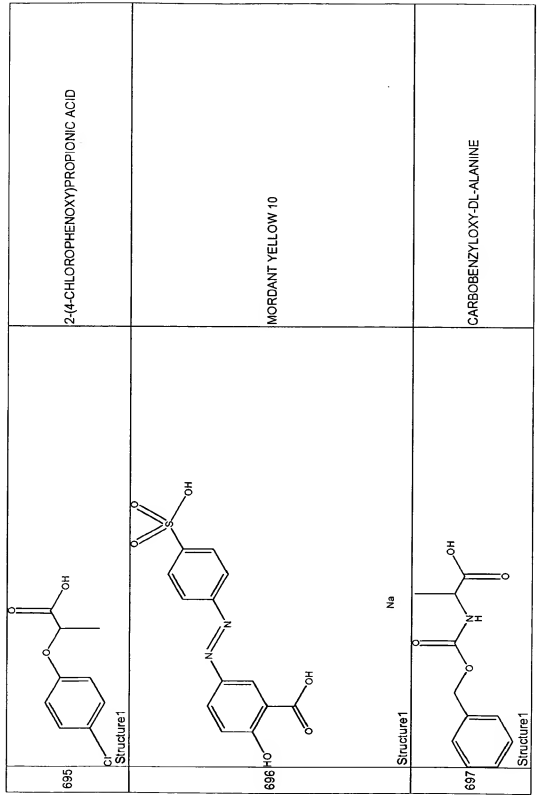

695
Structure1
2-(4-CHLOROPHENOXY)PROPIONIC ACID
696
Structure1
MORDANT YELLOW 10
697
Structure1
CARBOBENZYLOXY-DL-ALANINE

FIG. 4-GH

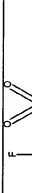
698	 Structure1	4-HYDROXYBENZOIC ACID
699	Structure1	4'-(TRIFLUOROMETHYL)-2-BIPHENYLCARBOXYLIC ACID
700	 Structure1	PENTAFLUOROBENZENESULFONYL CHLORIDE
701	Structure1	3-(4-CHLOROBENZOYL)PROPIONIC ACID

FIG. 4-GI

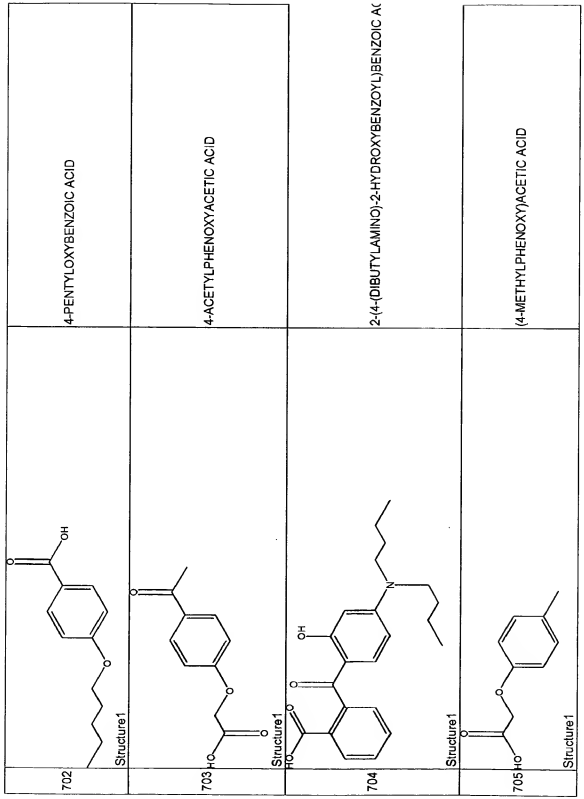

702
4-PENTYLOXYBENZOIC ACID
Structure1
703
4-ACETYLPHENOXYACETIC ACID
Structure1
704
2-(4-(DIBUTYLAMINO)-2-HYDROXYBENZOYL)BENZOIC AC
Structure1
705
(4-METHYLPHENOXY)ACETIC ACID
Structure1

FIG. 4-GJ

706	Structure1	4-NITROBENZENESULFONYL CHLORIDE
707	Structure1	2-(4-NITROPHENYL)PROPIONIC ACID
708	Structure1	4-ACETAMIDOBENZOIC ACID
709	Structure1	BUTYLPHOSPHONIC DICHLORIDE

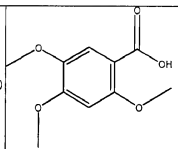
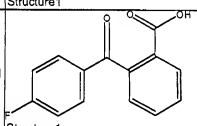
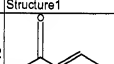
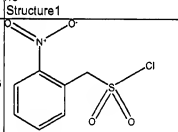
710	 Structure1	2,4,5-TRIMETHOXYBENZOIC ACID
711	 Structure1	2-(4-FLUOROBENZOYL)BENZOIC ACID
712	 Structure1	CROTONIC ACID
713	 Structure1	2-NITRO-ALPHA-TOLUENESULFONYL CHLORIDE

FIG. 4-GK

FIG. 4-GL

714	Structure1	NIFLUMIC ACID
715	Structure1	2-(4-CHLOROPHENOXY)-2-METHYLPROPIONIC ACID
716	Structure1	5-MERCAPTO-1-TETRAZOLEACETIC ACID, SODIUM SALT

FIG. 4-GM

717		2,3:4,6-DI-O-ISOPROPYLIDENE-2-KETO-L-GULONIC ACID
718	Structure1	HEXAFLUOROGLUTARIC ANHYDRIDE
719	Structure1	2-THIOPHENESULFONYL CHLORIDE
720	Structure1	2-BROMOBENZENESULFONYL CHLORIDE

FIG. 5-A

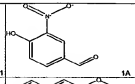
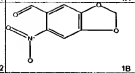
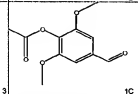
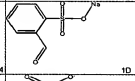
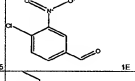
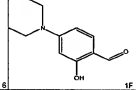
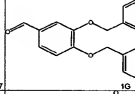
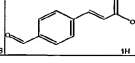
1	 1A	4-HYDROXY-3-NITROBENZALDEHYDE
2	 1B	6-NITROPIPERONAL
3	 1C	4-ACETOXY-3,5-DIMETHOXYBENZALDEHYDE
4	 1D	2-FORMYLBENZENESULFONIC ACID, SODIUM SALT HYDRATE
5	 1E	4-CHLORO-3-NITROBENZALDEHYDE
6	 1F	4-(DIETHYLAMINO)SALICYLALDEHYDE
7	 1G	3,4-DIBENZYLOXYBENZALDEHYDE
8	 1H	4-FORMYLCINNAMIC ACID

FIG. 5-B

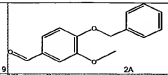
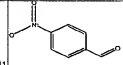
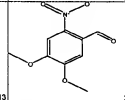
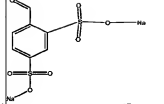
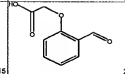
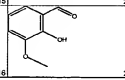
9	 2A	4-BENZYLOXY-3-METHOXYBENZALDEHYDE
10	 2B	1,8-NAPHTHALALDEHYDIC ACID
11	 2C	4-NITROBENZALDEHYDE
12	 2D	2-AMINO-3,5-DIBROMOBENZALDEHYDE
13	 2E	6-NITROVERATRALDEHYDE
14	 2F	4-FORMYL-1,3-BENZENEDISULFONIC ACID, DISODIUM SALT HYDRATE
15	 2G	2-FORMYLPHENOXYACETIC ACID
16	 2H	O-VANILLIN

FIG. 5-C

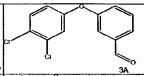
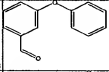
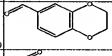
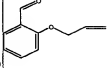
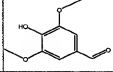
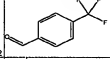
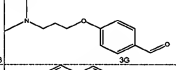
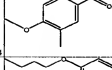
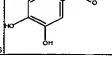
17		3A	3-(3,4-DICHLOROPHENOXY)BENZALDEHYDE
18		3B	3-PHENOXYBENZALDEHYDE
19		3C	1,4-BENZODIOXAN-6-CARBOXALDEHYDE
20		3D	2-ALLYLOXYBENZALDEHYDE
21		3E	SYRINGALDEHYDE
22		3F	ALPHA,ALPHA,ALPHA-TRIFLUORO-P-TOLUALDEHYDE
23		3G	4-(3-DIMETHYLAMINOPROPOXY)BENZALDEHYDE
24		3H	3-METHYL-P-ANISALDEHYDE
25		4A	4-BUTOXYBENZALDEHYDE
26		4B	3,4-DIHYDROXYBENZALDEHYDE

FIG. 5-D

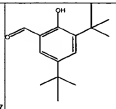
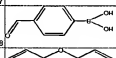
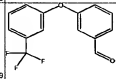
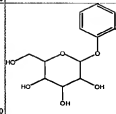
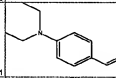
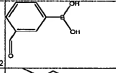
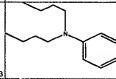
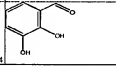
27		4C	3,5-DI-TERT-BUTYL-2-HYDROXYBENZALDEHYDE
28		4D	4-FORMYLPHENYLBORONIC ACID
29		4E	3-(3-(TRIFLUOROMETHYL)PHENOXY)BENZALDEHYDE
30		4F	HELICIN
31		4G	4-(DIETHYLAMINO)BENZALDEHYDE
32		4H	3-FORMYLPHENYLBORONIC ACID
33		5A	4-(DIBUTYLAMINO)BENZALDEHYDE
34		5B	2,3-DIHYDROXYBENZALDEHYDE

FIG. 5-E

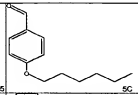
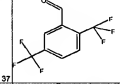
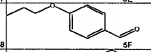
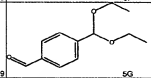
35		5C	4-HEXYLOXYBENZALDEHYDE
36		5D	2-FORMYLPHENYLBORONIC ACID
37		5E	2,5-BIS(TRIFLUOROMETHYL)BENZALDEHYDE
38		5F	4-PROPOXYBENZALDEHYDE
39		5G	TEREPHTHALALDEHYDE MONO-(DIETHYL ACETAL)
40		5H	3-CARBOXYBENZALDEHYDE
41		6A	3-HYDROXY-4-NITROBENZALDEHYDE
42		6B	3,4,5-TRIHYDROXYBENZALDEHYDE MONOHYDRATE

FIG. 5-F

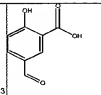
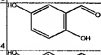
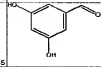
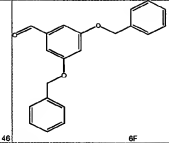
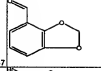
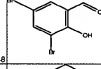
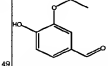
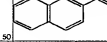
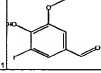
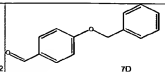
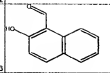
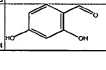
43		6C	5-FORMYLSALICYLIC ACID
44		6D	2,5-DIHYDROXYBENZALDEHYDE
45		6E	3,5-DIHYDROXYBENZALDEHYDE
46		6F	3,5-DIBENZYLOXYBENZALDEHYDE
47		6G	2,3-(METHYLENEDIOXY)BENZALDEHYDE
48		6H	3,5-DIBROMOSALICYLALDEHYDE
49		7A	3-ETHOXY-4-HYDROXYBENZALDEHYDE
50		7B	2-NAPHTHALDEHYDE
51		7C	5-IODOVANILLIN

FIG. 5-G

52	 7D	4-BENZYLOXYBENZALDEHYDE
53	 7E	2-HYDROXY-1-NAPHTHALDEHYDE
54	 7F	2,4-DIHYDROXYBENZALDEHYDE